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Contents

Page

The Course of Mitral Stenosis without Surgery: Ten- and Twenty-Year Perspectives. JOHN C. ROWE, EDWARD F. BLAND, HOWARD B. SPRAGUE and PAUL D. WHITE 741
Obesity and Diabetes: A Reëvaluation. S. K. FINEBERG 750
Some Observations on the Use of Chlorpropamide in Primary Tolbutamide-Failure Diabetics. LEO L. MORGENSTERN 761
On the Incidence of Senile Osteoporosis. RICHMOND W. SMITH, JR., WILLIAM R. EYLER and RAYMOND C. MELLINGER 773
Percutaneous Splenoportal Venography, with Additional Comments on Transhepatic Venography. SHERWIN S. ZEID, BENJAMIN FELSON and LEON SCHIFF 782
The Place of Corticotropin in the Treatment of Myasthenia Gravis. LEO D. FREYDBERG 806
The Significance of Lateral and Generalized Retinal Sheen. FRANK A. FINNERTY, JR., WILLIAM D. FOOTE, G. DECARLO MASSARO, JOHN TUCKMAN, JOACHIM H. BUCHHOLZ and MARTIN J. RYAN 819
Brucellosis: Experiences with 224 Patients. ALEXANDER SCHIRGER, DONALD R. NICHOLS, WILLIAM J. MARTIN, WILLIAM E. WELLMAN and LYLE A. WEED 827
Hyperinsulinism Secondary to Disease of the Pancreas and Organs Adjacent to the Pancreas: A Review of the World Literature. ERNEST O. FRIEDLANDER 838
Systemic Lupus Erythematosus and Hypertension without Renal Insufficiency. ALTON I. SUTNICK, ALFRED M. SELLERS, WILLIAM A. JEFFERS and CHARLES C. WOLFERTH 849
Goiter and Myxedema Due to Iodide Administration. BENJAMIN BURROWS, ALBERT H. NIDEN and WILLIAM R. BARCLAY 858
Cardiac Injury Due to Nonpenetrating Chest Trauma. JAMES H. WATSON and WARREN M. BARTHOLOMAE 871
An Address:
The Uses of Elegance. DANA W. ATCHLEY 881
Case Reports:
Association of Myasthenia Gravis and Hyperthyroidism, Showing Reciprocal Relationship: Report of a Case and Review of the Literature. JACOB JOHN ROBBINS and JOSEPH S. BURKLE 890
Idiopathic Retroperitoneal Fibrosis Associated with a Coagulation Defect (Factor VII Deficiency): Report of a Case and Review of the Literature. BERNARD I. POPHAM and THOMAS D. STEVENSON 894
Thrombocytopenia Associated with the Administration of Diethylstilbestrol in Man. BERNARD A. COOPER and FREDERICK S. BIGELOW 907
Pachymeningitis Apparently Due to Penicillin Hypersensitivity. LAURENCE FARMER, FRANCIS A. ECHLIN, WINIFRED C. LOUGHLIN, ARNOLD S. BREAKEY and ROGER DUVOISIN 910
Hemorrhagic Pericardial Fluid in Acute Benign Nonspecific Pericarditis: Report of a Case and Review of the Literature. CEILOUS L. WILLIAMS, JR., JULIAN R. BECKWITH and J. EDWIN WOOD, JR. 914
Fatal "Waterhouse-Friderichsen Syndrome" Due to Dicumarol. RONALD G. FRAGGE, I. LEONARD BERNSTEIN and JAMES BELL 923
Editorial—Auto-immunization and Auto-antibodies 930
Reviews 940
Medical News xcvii

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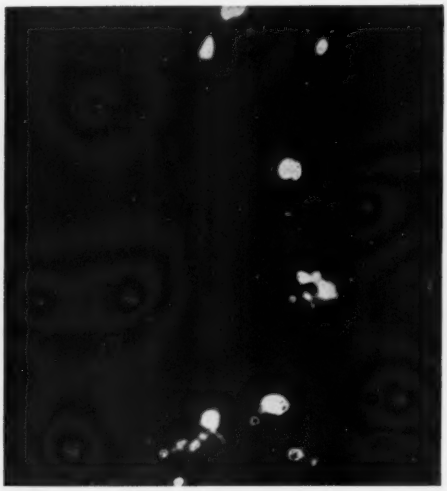
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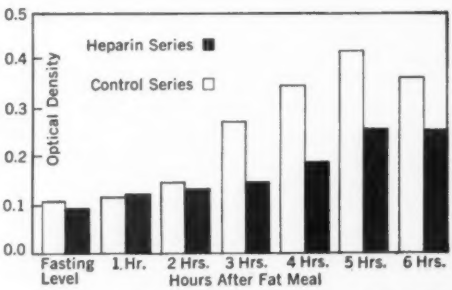
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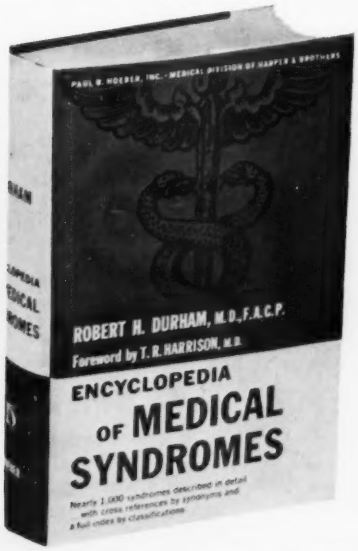
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1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.

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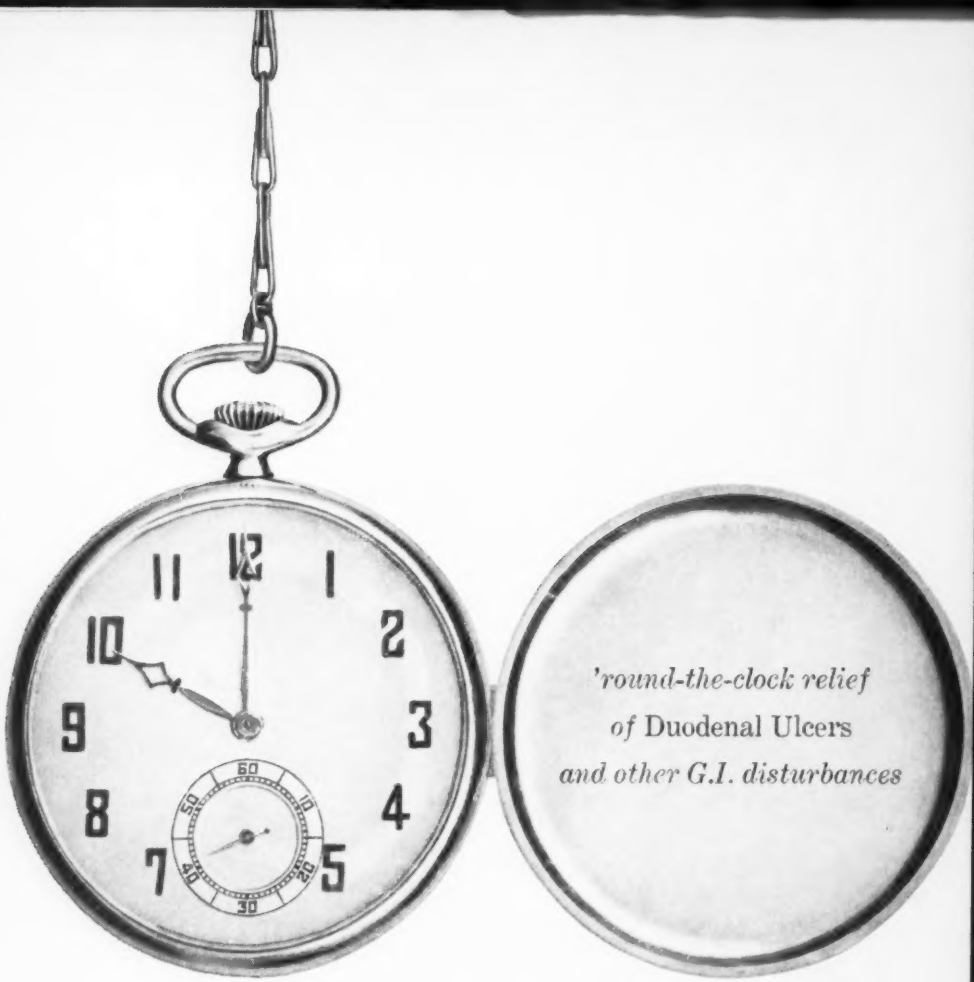
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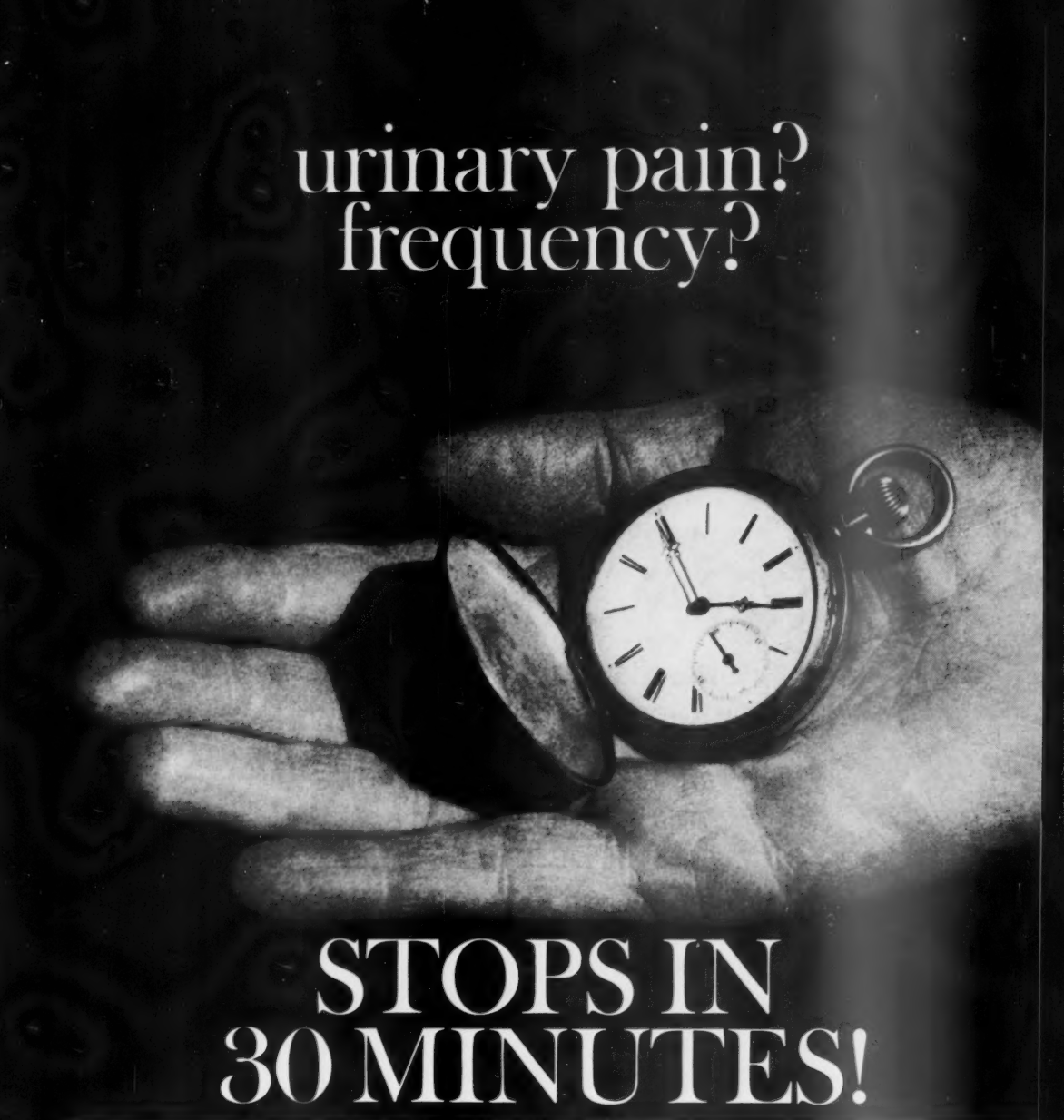
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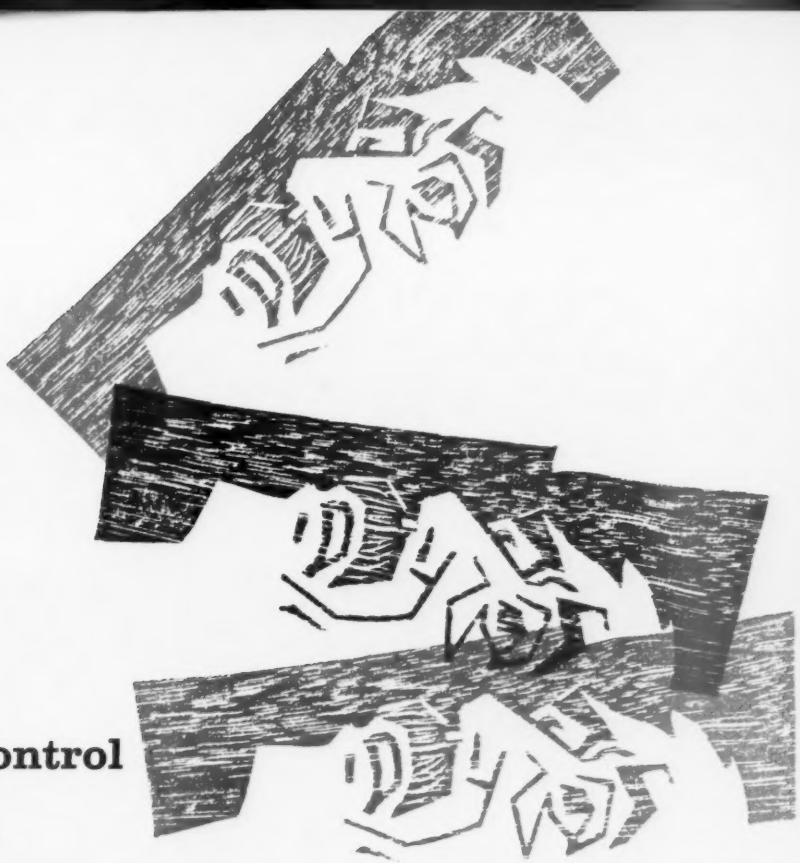
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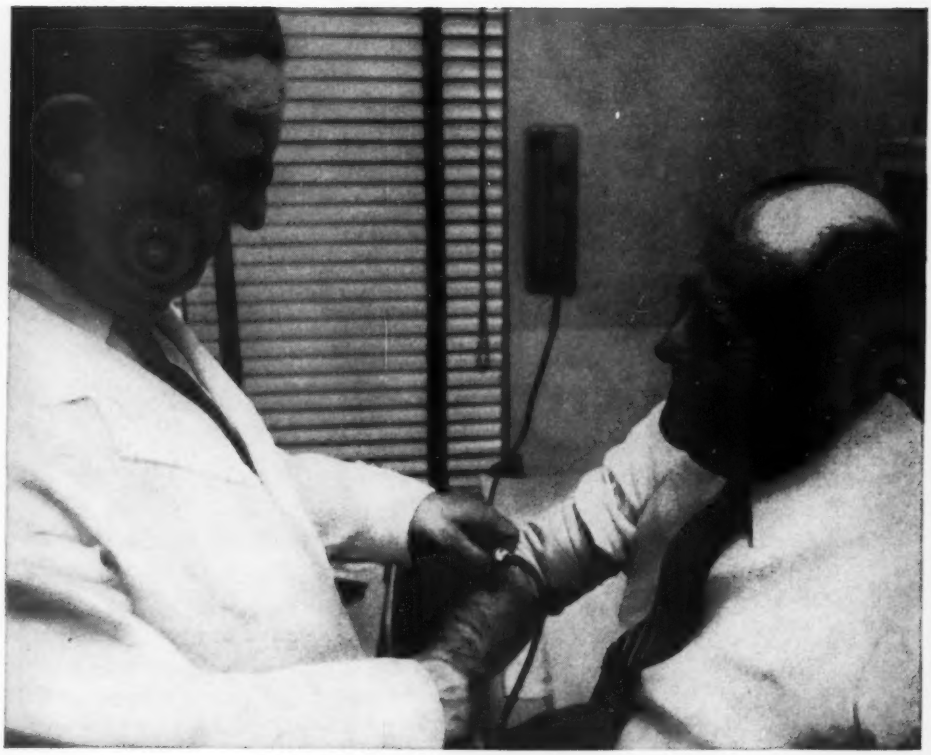
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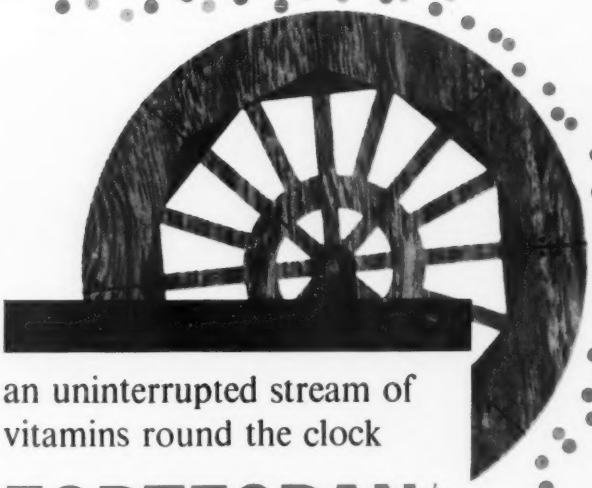
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2. Bartels, C. C.: N. E. J. Med. *261*:785 (Oct. 15) 1959.

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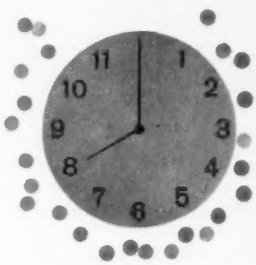
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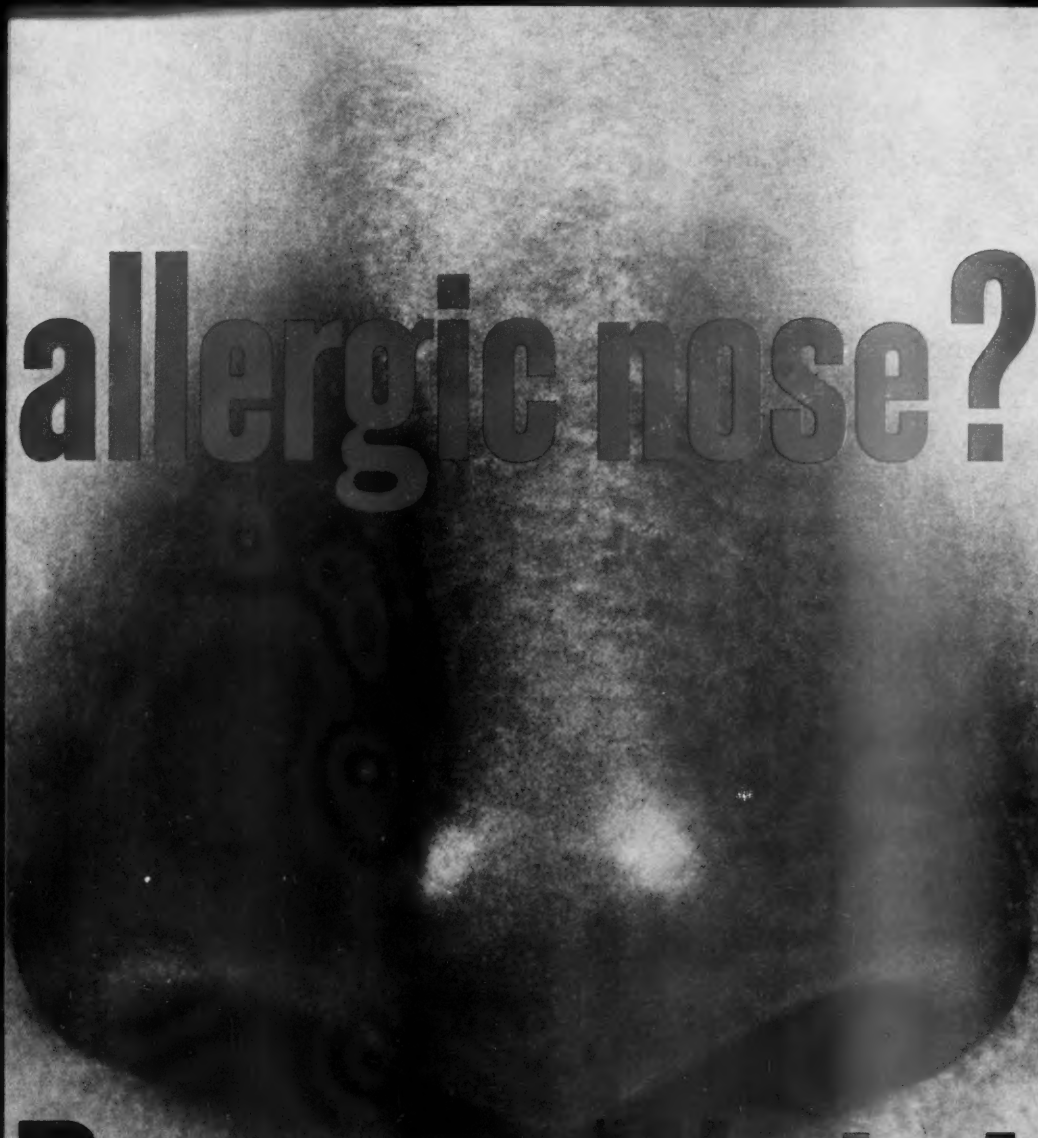
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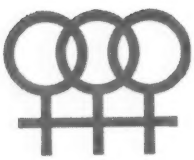
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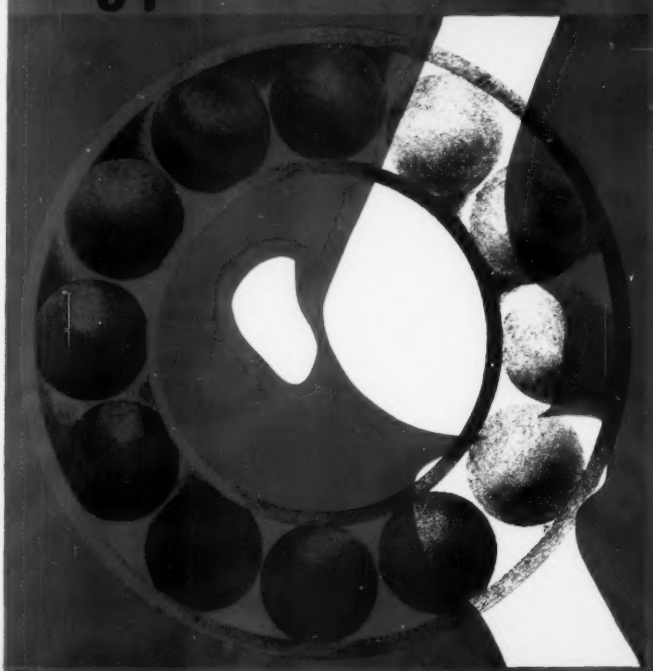
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Within 24 to 72 hours produces striking relief of pain.
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Butazolidin® (brand of phenylbutazone): Red-coated tablets of 100 mg.
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Modutrol allows complete and *lasting freedom* from symptoms—without dietary restrictions. Of all agents tested, only Modutrol achieved the three rigid objectives for success in peptic ulcer therapy: relief of symptoms, healing of ulcer and prevention of recurrences or complications. Moreover, Modutrol met these criteria in over 96 per cent of all patients tested.[1]

Psychophysiologic Medication To Combat A "Psychovisceral Process"

Therapeutic efficacy of Modutrol is enhanced by its psycho-active component, Sycotrol—proved clinically to be not only more effective than either sedatives or tranquilizers, but ideally suited for ambulatory patients because they do not experience commonly encountered side effects of depression and habituation. Sycotrol, a psychotropic agent with antiphobic properties, acts against fears and anxieties that find outlets in visceral manifestations. Modutrol combines the psycho-active agent with preferred antacid and anticholinergic therapy to provide total management of the disorder.

FORMULA: Each Modutrol tablet contains; Sycotrol (pipethanate hydrochloride) 2 mg., scopolamine methylnitrate 1 mg., magnesium hydroxide 200 mg., aluminum hydroxide 200 mg.

DOSAGE: One tablet 3 or 4 times daily.

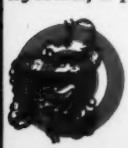
SUPPLIED: Bottles of 50 and 100 tablets.

CONTRAINDICATIONS: Contraindicated in glaucoma because of its anticholinergic components.

1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

Also available: Sycotrol tablets 3 mg. Bottles of 100 tablets.

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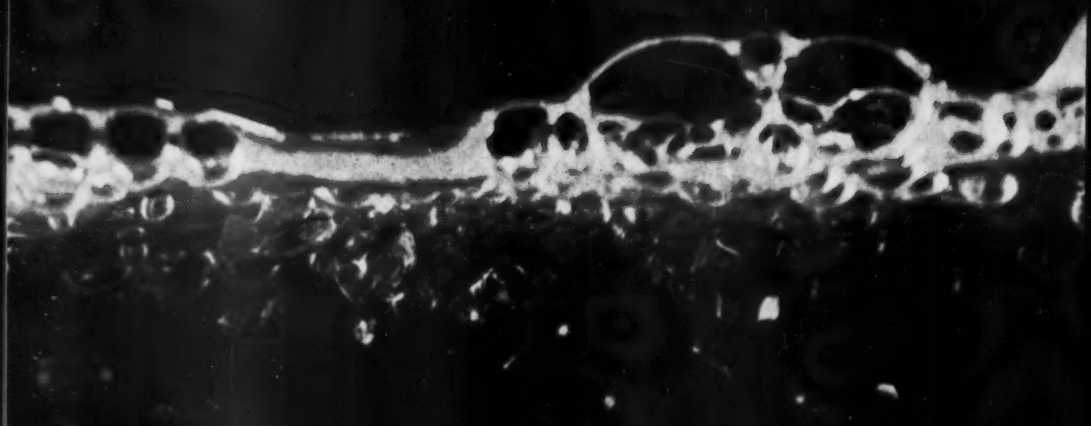


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Studying **ORETIC**, which they describe as ". . . a significant advance in development of diuretic agents of greater potency without increasing toxicity . . ." the investigators tested, among other properties of the compound, its clinical efficiency in long-term treatment of various edematous conditions.

Twenty patients were studied: eleven cardiacs, 3 nephrotics, 2 cirrhotics, 2 pregnancies (third trimester) and 2 "steroid" edematous patients.

Drug was given in 50-mg. dosages, daily for ninety days. Observations were made in the control state, and on the seventh, twenty-first and ninetieth days. Results were computed for body weight, serum electrolytes, blood urea, nitrogen and hematocrit:

CLINICAL RESPONSES TO ORETIC IN VARIOUS EDEMATOUS STATES

(Average Values for Each Group, Dose of 50 mg. daily)

Type of Edema	Number of pts.	Period	Cumulative Weight Loss (lbs.)	Serum (mEq/L) Na	K	CO_2 CP.*	Cl	BUN mg%	HCT.
Cardiac	11	Control		139	4.4	27	107	20	44
		Day 7	4	138	4.2	29	104	22	45
		Day 21	9	136	4.1	30	103	23	46
		Day 90	14	137	4.2	30	104	25	48
Nephrotic	3	Control		132	3.6	24	93	32	41
		Day 7	5	128	3.5	26	91	30	42
		Day 21	13	125	3.3	27	90	29	44
		Day 90	19.5	127	3.3	28	90	27	45
Cirrhotic	2	Control		131	3.2	26	88	9	39
		Day 7	6	130	2.7	25	86	10	42
		Day 21	15	128	2.6	26	85	11	41
		Day 90	22	128	2.7	26	84	10	42
Pregnancy	2	Control		144	4.2	27	106	11	40
		Day 7	2	143	4.1	28	102	13	41
		Day 21	5	142	4.1	31	99	13	43
"Steroid"	2	Control		146	3.5	32	94	14	38
		Day 7	3	145	3.3	33	89	15	42
		Day 21	6	143	3.0	33	87	17	43
		Day 90	9	142	3.1	34	88	17	43

*Co_2CP—Carbon Dioxide combining power

THE INVESTIGATORS SAID:

"The drug was effective in the therapy of edema, regardless of etiology, as seen from the data . . . All the groups had significant weight loss with the greatest loss occurring in the nephrotic and cirrhotic groups: except for the relief of the edema in all the patients observed, no other changes in clinical status were observed. Persistence of diuresis and the lack of additional toxicity in long term (90 days) therapy has been observed."

ORETIC, indicated for hypertension and edema, is supplied in 25- and 50-mg. tablets, bottles of 100 and 1000.

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Bibliographical Note: The study quoted has been published in the Sept., 1959, issue of *Current Therapeutic Research*, pp. 26-33.

ORETIC—TRADEMARK FOR HYDROCHLOROTHIAZIDE, ABBOTT

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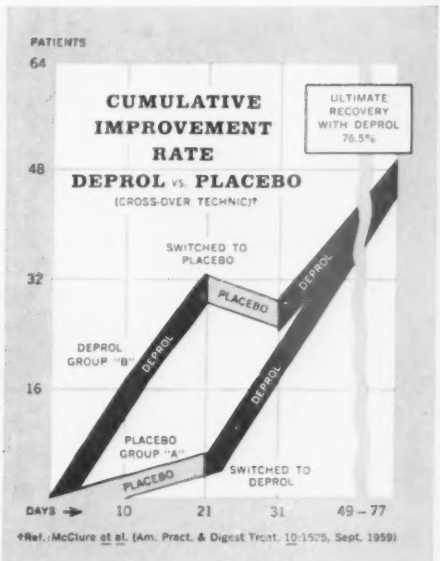
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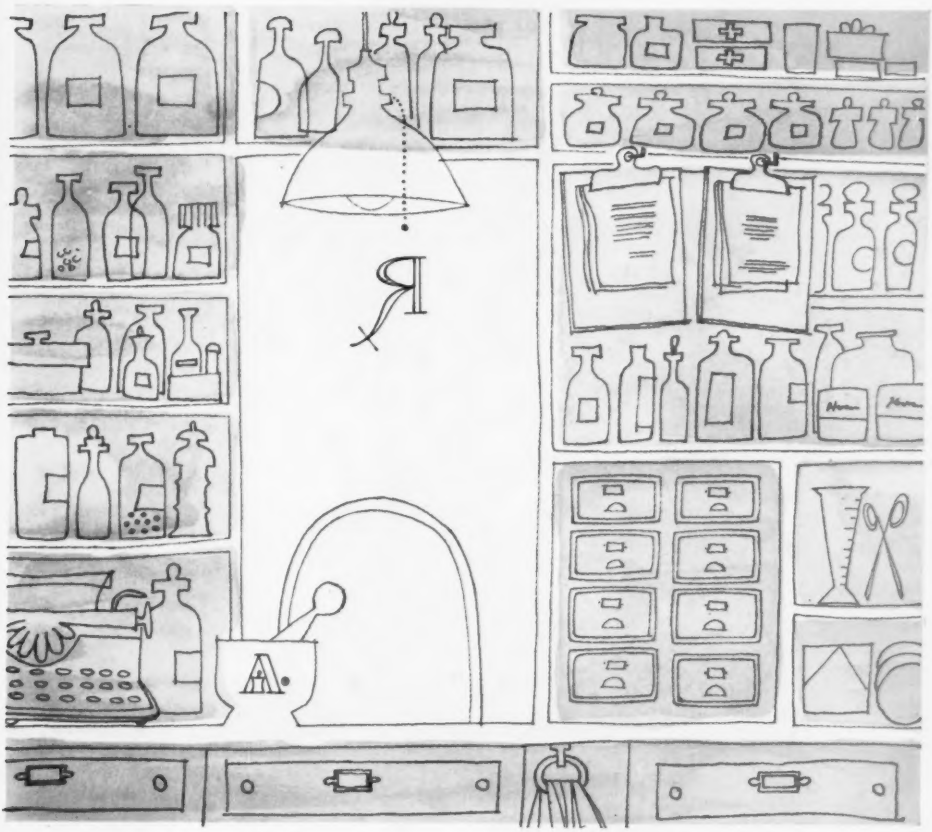
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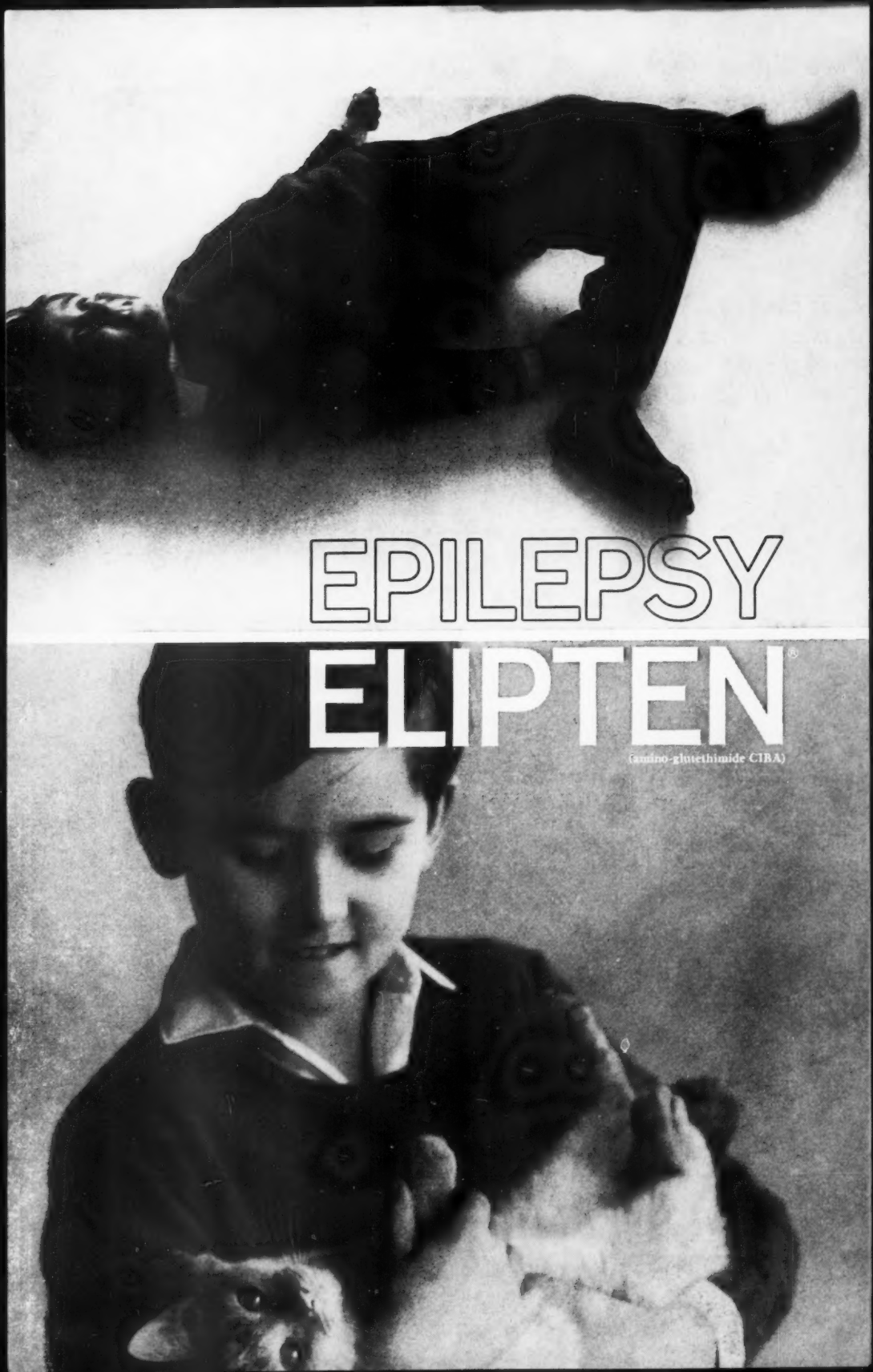
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Clinical Reports

Forster[1] states: "Elipten . . . has a definite role in improving the therapy, particularly of petit mal epilepsy." He notes further that Elipten ". . . oftentimes will turn the tide when added to partially successful medication." Meyer[2] observes: ". . . this drug is useful in generalized and localized convulsions as well as in status epilepticus. In addition, it is useful in the control of petit mal epilepsy and is of particular benefit in those cases where petit mal and generalized convulsions are combined. We have found it less useful in temporal lobe seizures." Lambros[3] notes complete control or marked improvement in 27 of 35 patients treated with Elipten (13 were gradually switched to Elipten alone; 14 were given other anticonvulsants adjunctively). Niswander and Karacan[4] report that in 38 hospitalized psychotic epileptic patients given Elipten, grand mal seizures were reduced 25 to 35 per cent. Carter[5] recommends concomitant use of Elipten and diphenylhydantoin sodium ". . . to enhance effectiveness and reduce the dosage of both drugs."

While most investigators report that a transient skin rash occurs in some patients, especially when initial dosage is high, Sheehan[6] states: "On reduction of the dose, this rash quickly disappears and does not recur when the dose is gradually stepped up to its original level." Forster[1] also notes that ". . . this [the rash] is not a serious complication and does not rule out Elipten therapy."

Complete information on Elipten is available on request.

SUPPLIED: *Tablets,* 250 mg. (white, scored); bottles of 100.

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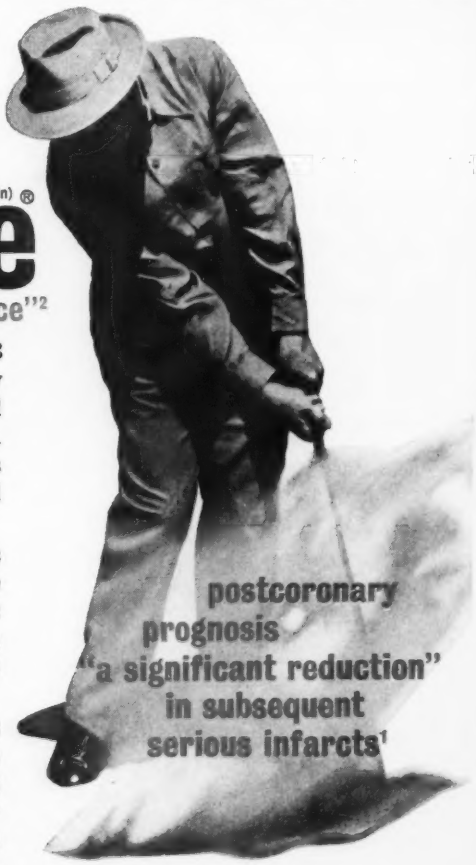
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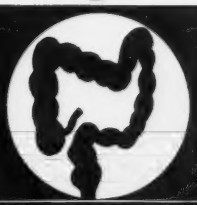


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what is the incidence of gallbladder disease in "normal" men?

Studies showed gallbladder abnormalities in 14.6 per cent of a group of 1,233 active men in the productive years of their lives.*

*Wilbur, R. S., and Bolt, R. J.: Gastroenterology *36*:251, 1959.

Cholecystogram Findings in 1233 "Normal" Men*

Category	Number	Average Age, years
Normal cholecystogram	1051	46.26
Postcholecystectomy	25	51
Faint visualization	45	50.6
Nonvisualization	20	51.6
Biliary calculi	92	48.3
Total abnormal	182	49.9

*Adapted from Wilbur, R. S., and Bolt, R. J.

in medical and pre- and postoperative management of biliary tract disorders...

• for free-flowing *therapeutic* bile — DECHOLIN®
(dehydrocholic acid, AMES)

• for true hydrocholeresis *plus* reliable spasmolysis — DECHOLIN® with Belladonna

Available: DECHOLIN tablets: (dehydrocholic acid, AMES) 3¾ gr. (250 mg.).
Bottles of 100, 500 and 1,000.

DECHOLIN/Belladonna tablets: DECHOLIN (dehydrocholic acid, AMES) 3¾ gr. (250 mg.) and extract of belladonna ⅙ gr. (10 mg.).
Bottles of 100 and 500.

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specific treatment for arthritic joints

intra-articular/intrasynovial/intrabursal instillation

□ **good to excellent response in a vast majority of patients**—"Low doses...provided rapid and effective relief...in almost all of the 157 patients treated..."[1] "...appeared to be superior as an intra-articular injectable substance to anything hitherto available."[2]

□ **provides sustained, long lasting benefits**—In 28 out of 34 patients,"...complete relief was provided by a single injection...the relief lasting for an average of more than 2.5 months."[2]

□ **rapid relief of pain, swelling, and improved range of motion**—"Pain was relieved in 3 or 4 days, or less..."[3] "...marked improvement in range of motion occurred in all of these patients."[3] "...more potent, milligram for milligram, than other injectable corticosteroids."[4]

□ **undesirable side reactions outstandingly rare**—"...appears to be a safe, potent, and effective preparation..."[5] "...tolerated as well as or better than hydrocortisone or prednisolone."[6]

Dosage: usual doses—2.5 to 5.0 mg. for smaller joints; 5.0 to 15.0 mg. for larger joints. *Side Effects:* outstandingly rare; although systemic effects do not ordinarily occur with Kenalog Parenteral when the proper techniques and dosages are used, careful clinical supervision is advisable for all patients receiving steroid therapy. *Contraindications:* infections in or near joints—e.g., gonococcal or tuberculous arthritis. *Supply:* a sterile aqueous suspension in 5 cc. vials, each cc. providing 10 mg. triamcinolone acetonide. *References:* 1. Sperling, I. L.: Clinical Research Notes vol. 3, No. 1 (Jan.) 1960. 2. Steinberg, C. L.: op. cit. 3. Urist, M. R.: op. cit. 4. Meltzer, L. E.: op. cit. 5. Schwartz, S.: op. cit. 6. Felts, W. R.: op. cit.

Among 363 patients treated with Kenalog Parenteral, 315 (86.7%) obtained complete relief or were markedly improved.[1-6]

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FOR PROVEN MENOPAUSAL BENEFITS



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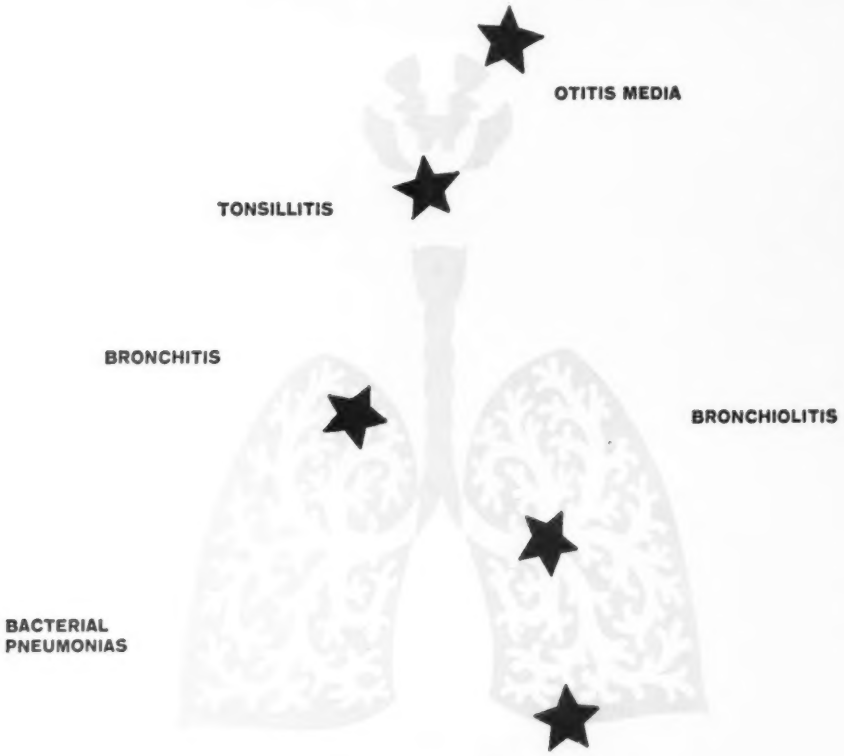
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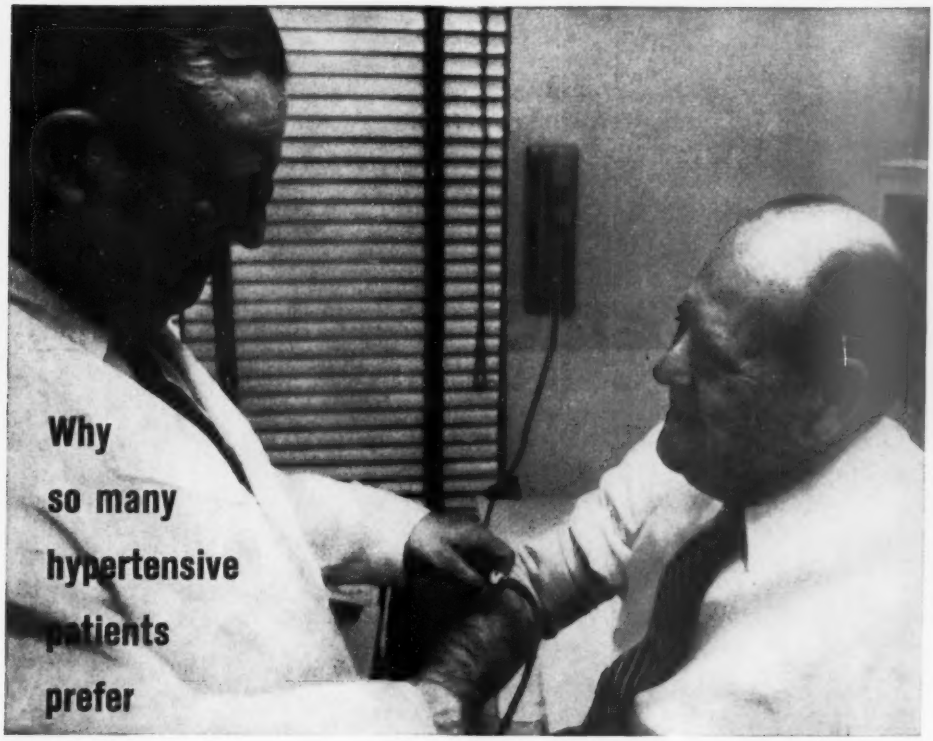
effective perorally against the majority of common infections caused by pathogenic bacteria including the antibiotic-resistant staphylococci

ALTAFUR is available in tablets of 250 mg. (adult) and 50 mg. (pediatric), bottles of 20 and 100.

1. Lysaught, J. N., and Cleaver, W.: Proceedings of the Detroit Symposium on Antibacterial Therapy (Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959).

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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

Singoserp®

(syrosingopine CIBA)

First drug to try in new hypertensive patients

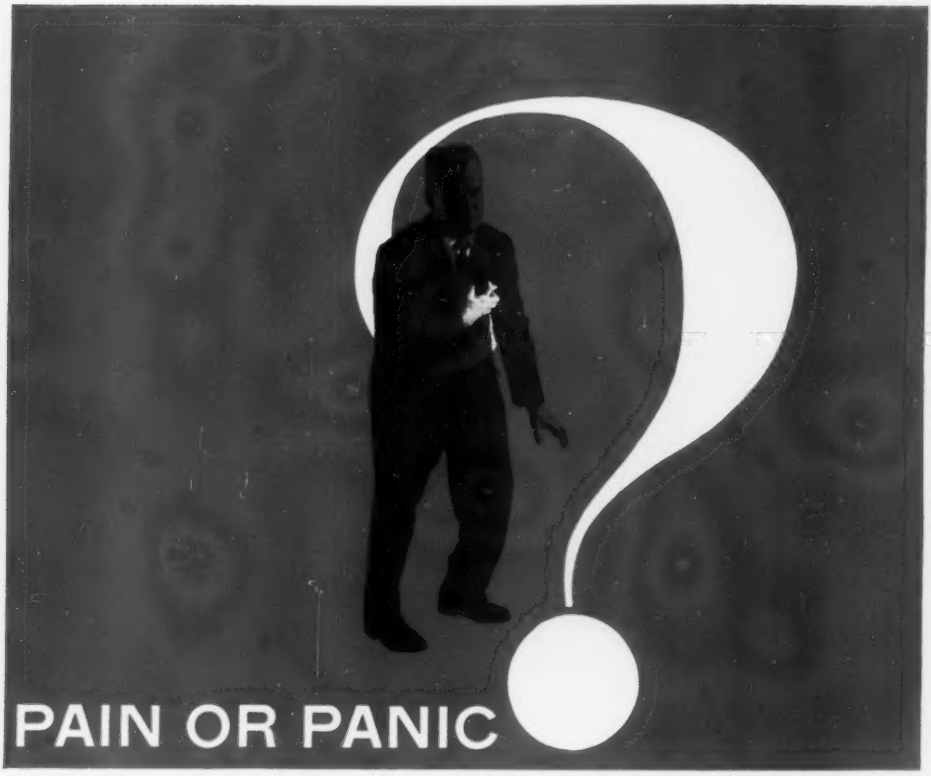
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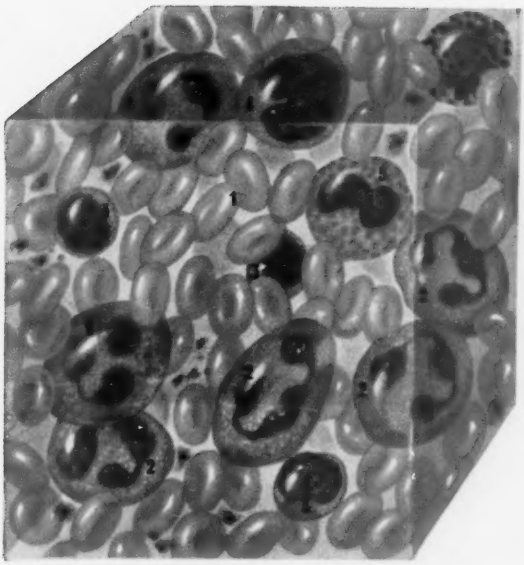
CARTRAX®

Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX). For convenience, write "CARTRAX 10" or "CARTRAX 20." **Supplied:** In bottles of 100. Prescription only.

References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

*brand of hydroxyzine

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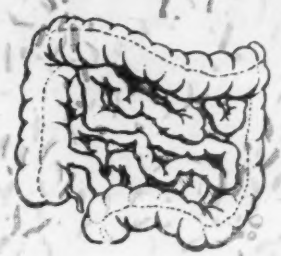
White Laboratories, Inc., Kenilworth, New Jersey

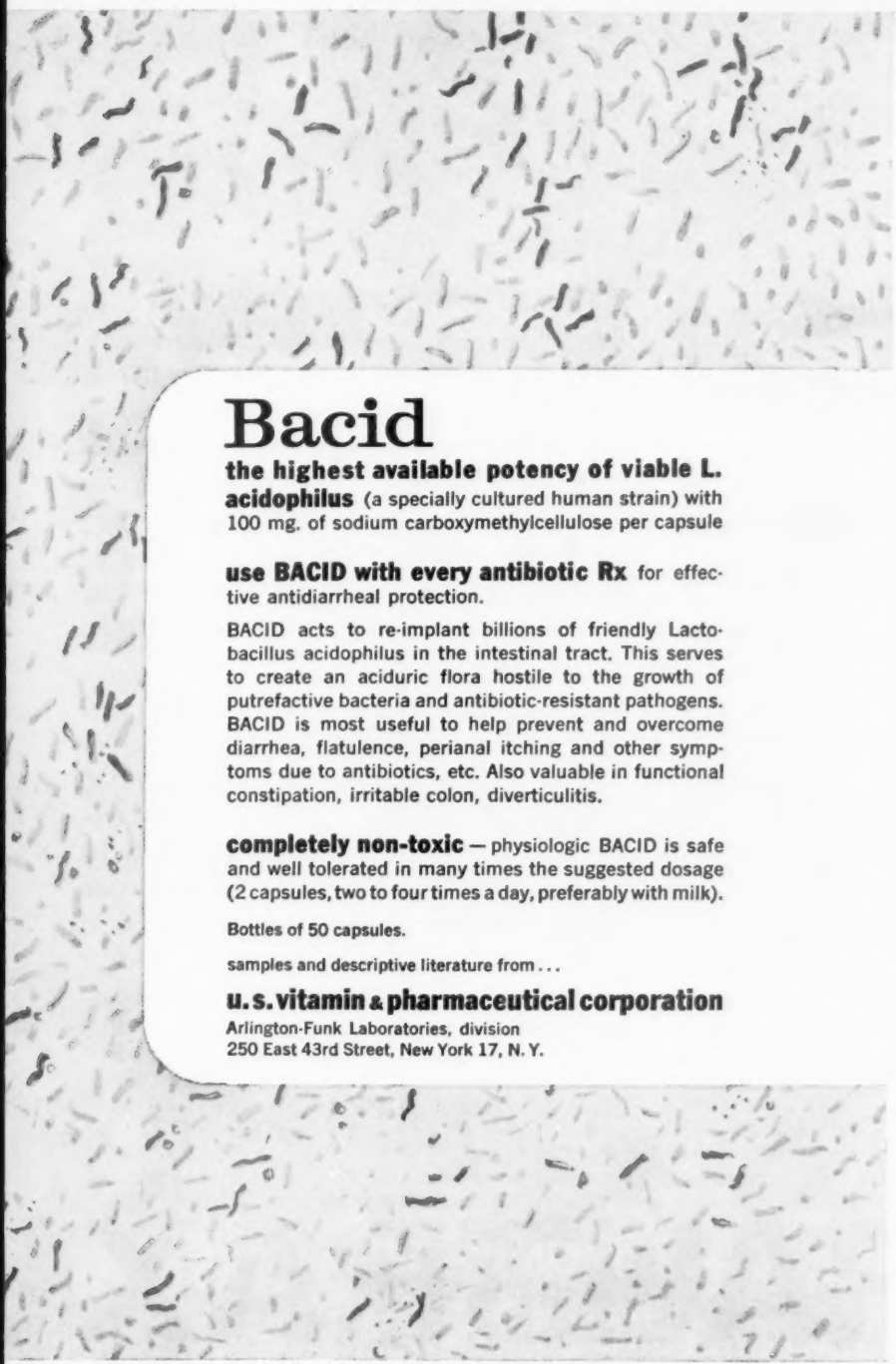
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clear up
antibiotic-caused diarrhea

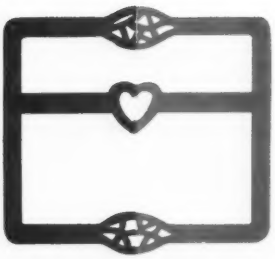
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the highest available potency of viable L. acidophilus (a specially cultured human strain) with 100 mg. of sodium carboxymethylcellulose per capsule
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The dependable diuretic action of Ademol rapidly controls the clinical and subclinical edema often associated with cardiovascular disease. And after Rautrax has normalized the fluid balance, the normal serum electrolyte pattern is not altered appreciably by continued administration.[4] Ademol also potentiates the antihypertensive action of Raudixin.[1] In this way a lower dose of each component controls hypertension effectively and safely . . . with fewer side effects.

REFERENCES: 1. Montero, A. C.; Rochelle, J. B., III, and Ford, R.V.: New England J. Med. 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: Am. J. Cardiol. 3:676 (May) 1959. 3. Fuchs, M., and others: Monographs on Therapy 4:43 (April) 1959. 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: Am. Heart J. 57:484 (April) 1959. 5. Rochelle, J. B., III; Montero, A. C., and Ford, R. V.: Antibiotic Med. & Clin. Ther. 6:267 (May) 1959. LITERATURE AVAILABLE ON REQUEST

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'RAUDIXIN' ®, 'RAUTRAX' AND 'ADEMOL' ARE SQUIBB TRADEMARKS



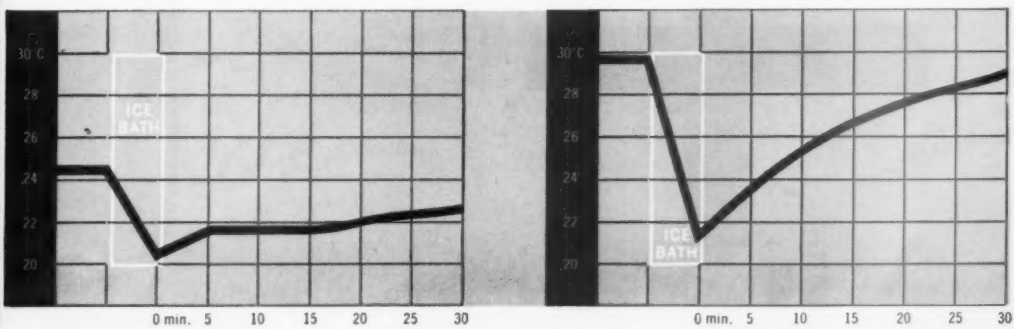
in peripheral vascular disease . . . direct, prolonged action

In both *vasospastic and occlusive* peripheral vascular diseases, CYCLOSPASMOL is orally effective, well tolerated, and notably free from side-effects. Clinically proved, it is recommended for the *control of intermittent claudication* in arteriosclerosis obliterans, Raynaud's disease, and Buerger's disease. *Also for treatment* of trophic and diabetic ulcerations and for circulatory impairment of feet, legs, and hands.

VASODILATING EFFECT OF CYCLOSPASMOL DEMONSTRATED BY THERMAL DATA[1]

Before CYCLOSPASMOL therapy—average skin temperature of fingertips of both hands

After CYCLOSPASMOL therapy (100 mg. q.i.d. for 2 weeks)—average skin temperature of fingertips of both hands



Patient is 65-year-old woman suffering from peripheral vascular disease attended by vasospasm. Before CYCLOSPASMOL, skin temperature remains almost constant following ice bath. Skin temperature climbs six degrees in the same interval, however, when patient is on CYCLOSPASMOL therapy.

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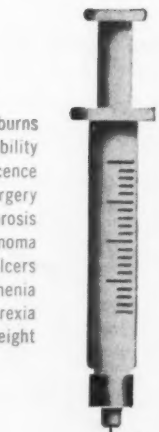
CYCLOSPASMOL®

Cyclandelate (3,5,5 trimethylcyclohexyl mandelate),
Ives-Cameron; U.S. Patent No. 2,707,193

Reference: 1. Kappert, A.: Schweiz. med. Wchnschr. 85:273, 1955. Bibliography: 1. Van Wijk, T.W.: Angiology 4:103, 1953. 2. Gilhespy, R.O.: Brit. M.J. 2:1543, 1957. 3. Gilhespy, R.O.: Angiology 7:27, 1956. 4. Winsor, T.: Angiology 4:134, 1953. 5. Reeder, J.J.: Geneesk. gids. 31:370, 1953.

1 cc. once each week

burns
debility
convalescence
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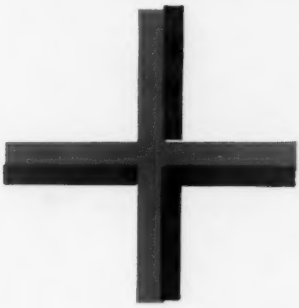


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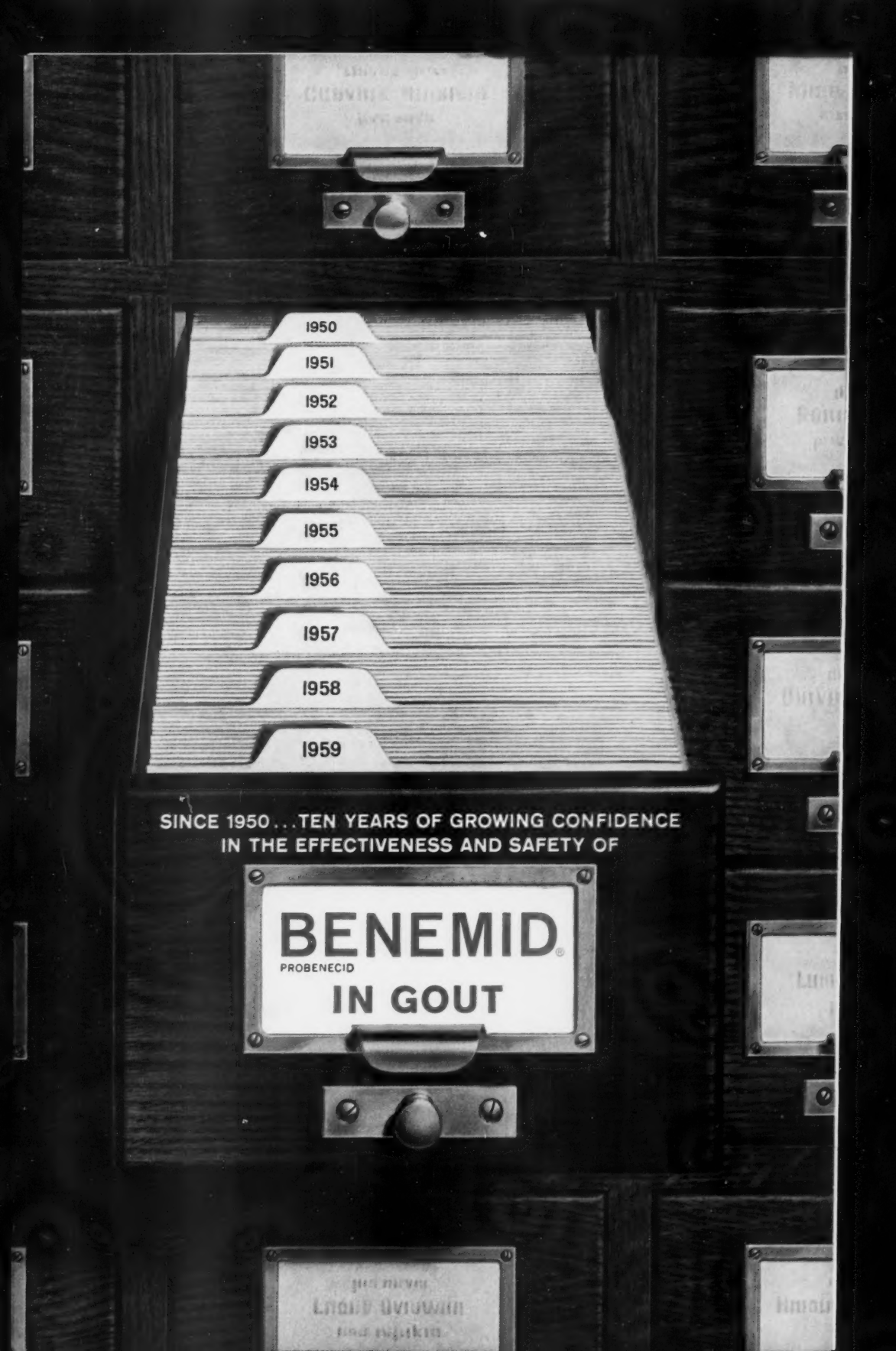
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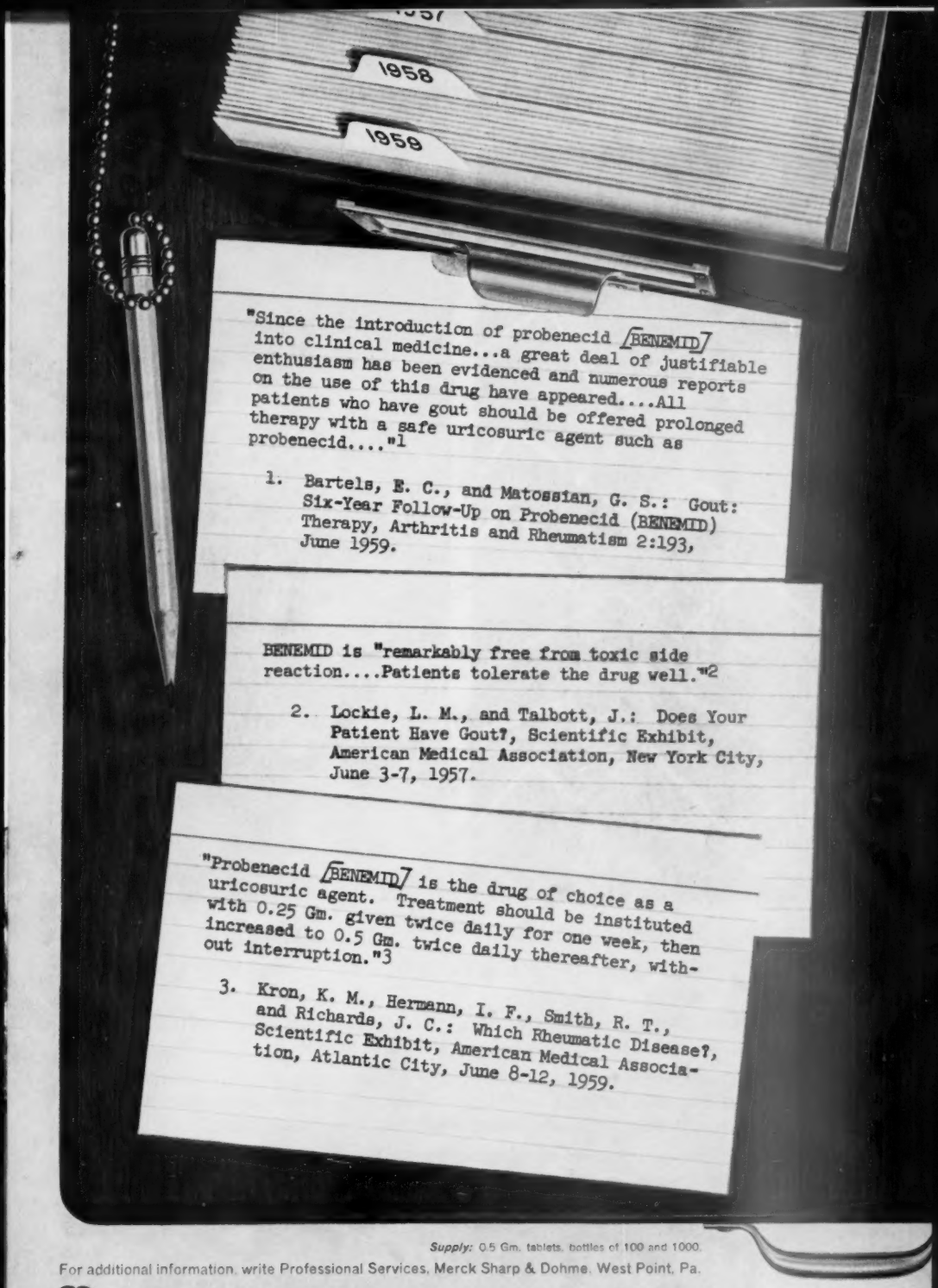


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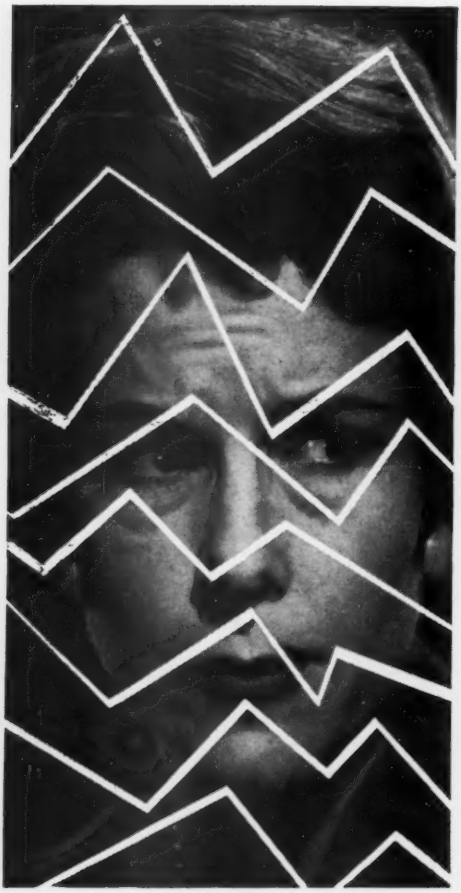


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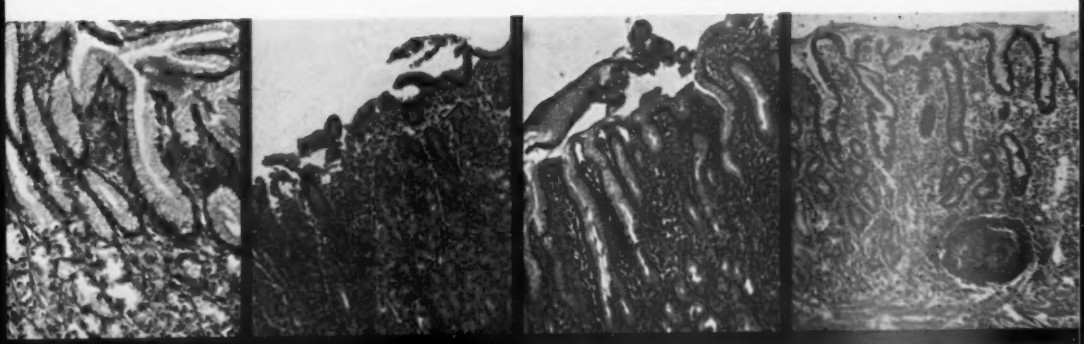
†Trademark for Tablets Protoveratrine A, 0.2 mg. and Reserpine, 0.08 mg. *Patent Pending

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GASTRITIS

a pathological entity

histologically demonstrable



NORMAL GASTRIC MUCOSA

MILD CHRONIC GASTRITIS

Reversible. Glandular pattern, muscularis well preserved.

MODERATE CHRONIC GASTRITIS

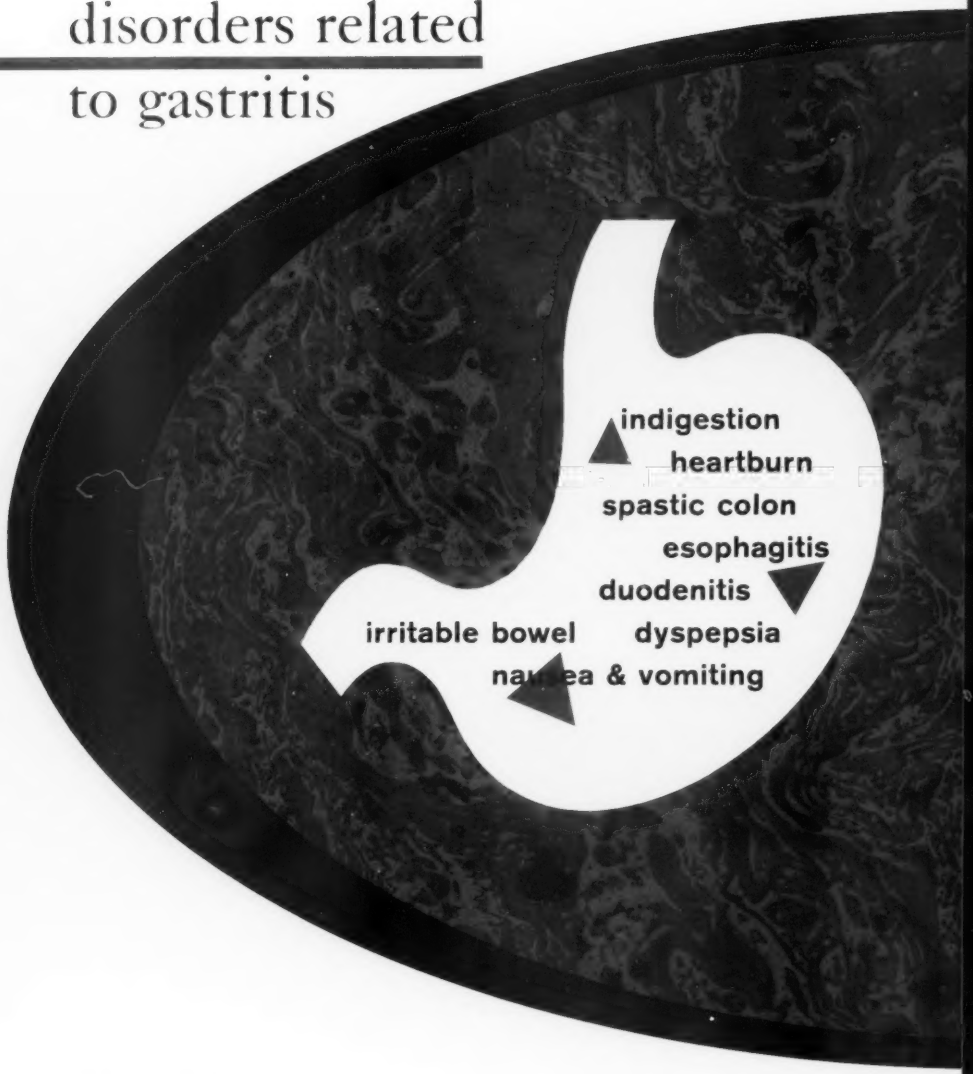
Reversible. Irregular distribution of glands. Early intestinalization of surface epithelium. Disruption of muscularis secondary to inflammatory process.

SEVERE CHRONIC GASTRITIS

Irreversible. Considerable distortion of glands. Mucous cells indicate conversion to colonic-type tissue. Fragmentation of muscularis.

Microscopic views of gastric biopsies, courtesy of E. Deutsch, M.D., originally published as part of study, Chronic Gastritis, Deutsch, E., and Christian, H. J.: J.A.M.A. 169:2012 (Apr. 25) 1959.

disorders related to gastritis



symptoms

Pain - Food - Pain—as opposed to Pain - Food - Relief in peptic ulcer

Persistent, generalized upper abdominal pain—as opposed to localized pain of peptic ulcer

Bloating, sensation of fullness when only a small amount of food has been ingested

Possible severe weight loss—40 to 80 pounds

treatment for gastritis

OXAINE*

Oxethazaine in Alumina Gel, Wyeth

containing a gastric mucosal anesthetic

an original development, result of 5 years' research and clinical trial

OXAINE is indicated for many gastric disorders, such as gastritis, which are not totally managed by diet, antacids and anticholinergics.

As reported in J.A.M.A., OXAINE brought *complete* relief to 96%, partial relief to 4%, of 92 patients suffering substernal pain and upper abdominal distress. *Deutsch, E., and Christian, H.J.: J.A.M.A.* 169:*2012 (Apr. 25) 1959.*

OXAINE provides sustained anesthesia over many hours, unaffected by ebb and flow of gastric contents.

Oxethazaine, the mucosal anesthetic in OXAINE, is 4000 times more potent topically than procaine. Safe, not a "caine." Only two known cases of sensitivity (glossitis) occurred in extensive clinical trials.

Easily administered, simple dosage regimen—just 1 or 2 tsp. 4 times daily, 15 minutes before meals and at bedtime.

Bland, noncloying over long-term administration.

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A Century of Service to Medicine

when the sequence of symptoms spells

PAIN
FOOD
PAIN

new

OXAINE*

Oxethazaine in Alumina Gel, Wyeth

a mucosal anesthetic for

GASTRITIS

Description: Each 5 cc. teaspoonful contains 10 mg. of oxethazaine [N,N-bis-(N-methyl-N-phenyl-t-butyl-acetamido)-beta-hydroxyethylamine] in alumina gel.

Dosage: Usual dosage is 1 or 2 teaspoonfuls 4 times daily, 15 minutes before meals and at bedtime.

Do not exceed recommended dosage.

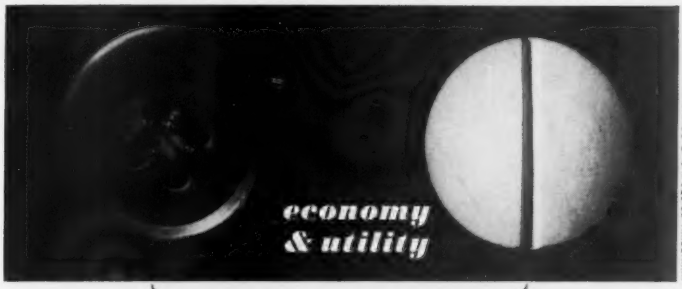
Supplied: Bottles of 12 fluidounces.

Limitations: In case of overdosage, dizziness, faintness or drowsiness may be experienced by some patients. Constipation may be aggravated by therapeutic doses of OXAINE, but can be mitigated by adequate fluid intake and use of dietary roughage or a mineral oil preparation.

The possibility of gastrointestinal carcinoma should be considered in patients with protracted or recurrent indigestion.

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clinically proved
oral penicillin therapy
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Pentids

Squibb Penicillin G Potassium

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Available in these convenient dosage forms: PENTIDS '400' TABLETS (400,000 u.) • PENTIDS '400' FOR SYRUP (400,000 u. per 5 cc. when prepared) • PENTIDS TABLETS (200,000 u.) • PENTIDS FOR SYRUP (200,000 u. per 5 cc. when prepared) • PENTID-SULFAS TABLETS (200,000 u. with 0.5 Gm. triple sulfas) • PENTIDS CAPSULES (200,000 u.) • PENTIDS SOLUBLE TABLETS (200,000 u.)

RETURN PATIENTS TO CONSCIOUSNESS FROM...



hepatic coma

associated with high blood ammonia levels

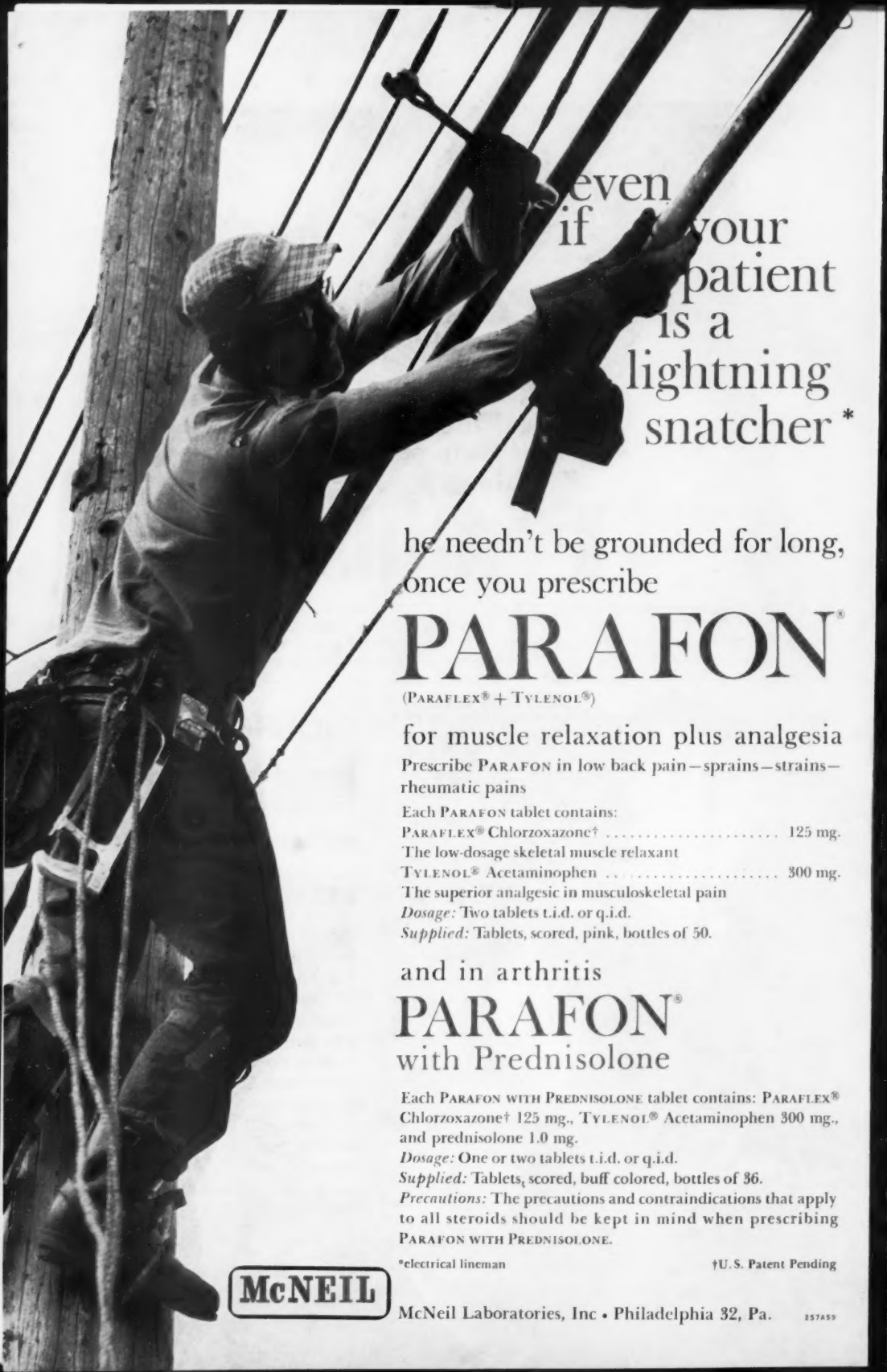
GLUTAVENE®
&
GLUTAVENE-K®

For the treatment of coma and other encephalopathies in certain liver diseases associated with high blood ammonia levels, Glutavene supplies monosodium l-glutamate and Glutavene-K supplies monosodium and monopotassium l-glutamate. These agents reduce ammonia blood levels through amidation, a reaction between glutamate and ammonia to form glutamine, a nontoxic substance.[1,2]

administration: For the average adult, 100 pounds or over, the contents of a 100 cc. (25 gram) vial are mixed with 1000 cc. of 5 or 10% glucose in water. This amount is given intravenously during a 4-hour period.

References: 1. McDermott, W. V., Jr.; Wareham, J., and Riddell, A. G.: New England J. Med. 253:1093 (Dec. 22) 1955. 2. Watson, C.: J.A.M.A. 166:764 (Feb. 15) 1958.

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Wayne, New Jersey



even if your patient is a lightning snatcher *

he needn't be grounded for long, once you prescribe

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(PARAFLEX® + TYLENOL®)

for muscle relaxation plus analgesia

Prescribe PARAFON in low back pain—sprains—strains—rheumatic pains

Each PARAFON tablet contains:

PARAFLEX® Chlorzoxazone† ..... 125 mg.
The low-dosage skeletal muscle relaxant

TYLENOL® Acetaminophen ..... 300 mg.
The superior analgesic in musculoskeletal pain

Dosage: Two tablets t.i.d. or q.i.d.

Supplied: Tablets, scored, pink, bottles of 50.

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New! ... for appetite control



Helps stop overeating

CURBS APPETITE ... RELIEVES DIET TENSIONS

This new anorectic gives you dextro-amphetamine to curb your patient's appetite. It also gives you Miltown to relieve the tensions of dieting which undermine her will power.

In prescribing Appetrol, you will find that your patient's bad eating habits are considerably improved — and that she will stay on the diet you prescribe.

Usual dosage: 1 or 2 tablets one-half to 1 hour before meals.

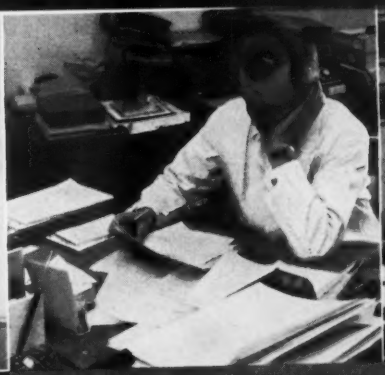
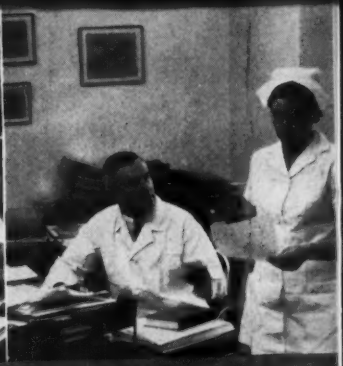
Each tablet contains: 5 mg. dextro-amphetamine sulfate and 400 mg. Miltown (meprobamate, Wallace).

Available: Bottles of 50 pink, scored tablets.

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PANWARFIN is predictable in its effect. The physician will note but little day-to-day fluctuation in his patients' prothrombin times. He isn't beset by the usual need for frequently readjusting dosage. Guided by simple lab determinations, he gains early control of coagulability, and maintains the dosage with a minimum of tinkering.

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Consider PANWARFIN for your future anticoagulant regimens, doctor. Our literature gives full details.

ASK YOUR ABBOTT REPRESENTATIVE FOR IT, OR WRITE.

SUPPLIED in 5-mg. white grooved tablets, List No. 6973, bottles of 100 and 1000; 10-mg. yellow grooved tablets, List No. 6988, bottles of 100 and 1000; and 25-mg. orange grooved tablets, List No. 6994, bottles of 25, 100, and 1000.

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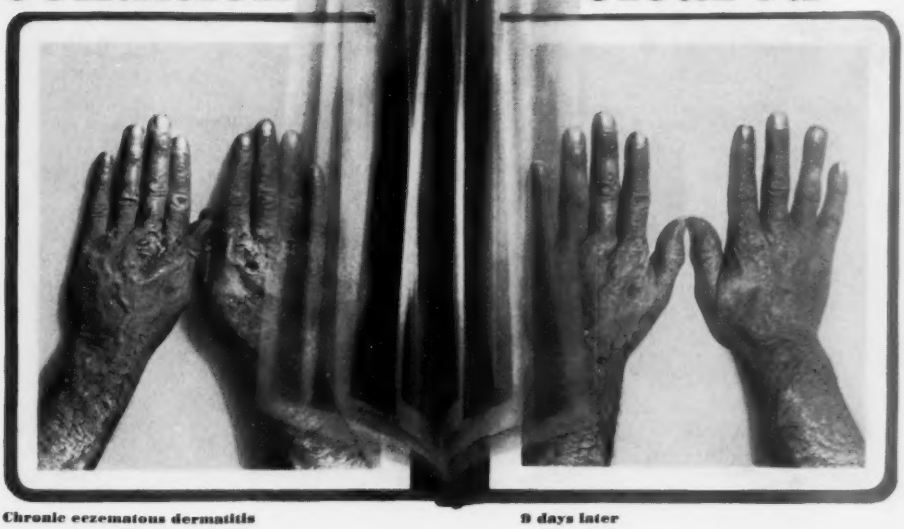
Pentritol Tempules given every 12 hours reduced or eliminated nitroglycerin requirements, stopped anginal attacks or reduced their frequency, eliminated or mitigated pain, and increased the capacity for physical activity. *Patients previously taking PETN in tablets with little progress, responded favorably to Pentritol Tempules.*[2]

Recommended dose is 1 Pentritol Tempule morning and evening, approximately 12 hours apart. Available in bottles of 60 Tempules. Also available: Pentritol-B Tempules with 50 mg. of butabarbital added for vasodilation *plus* sedation.

1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957. © 1960, A.P. Co.

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for extra protection against infection

Kenalog-S
Squibb Triamcinolone Acetonide with Neomycin and Gramicidin (Spectrocin)

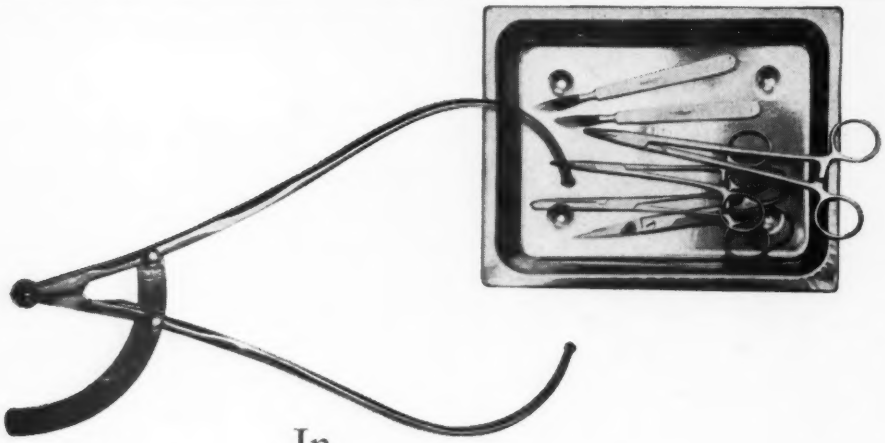
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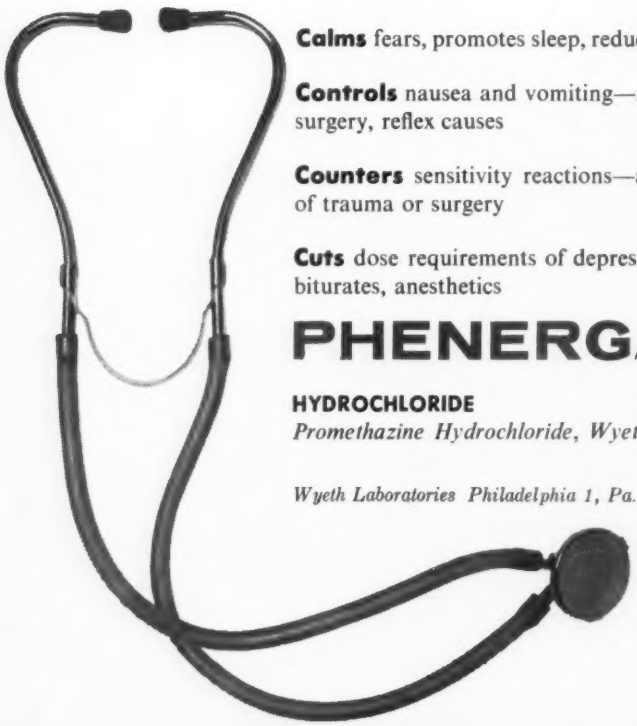
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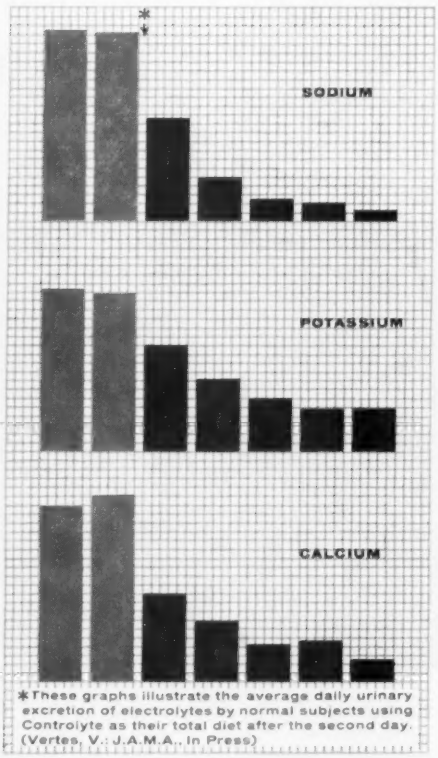
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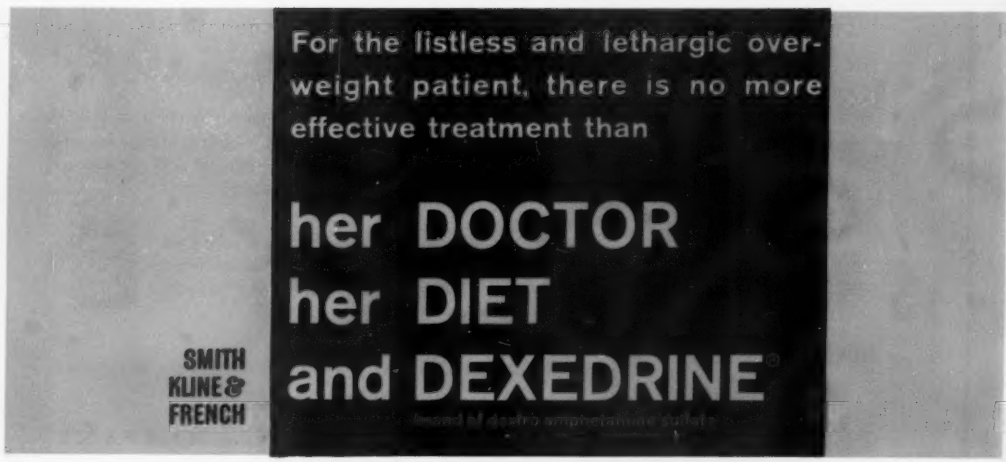
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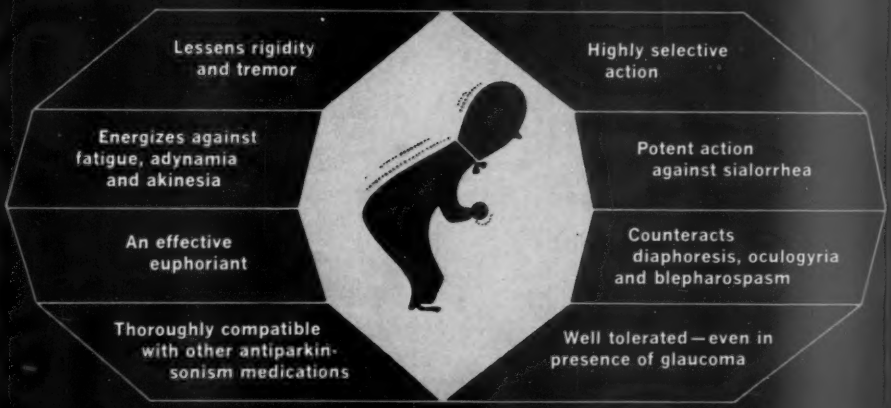
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Dosage: Usually 1 tablet (50 mg.) t.i.d. When used in combination, dosage should be correspondingly reduced.

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No known organic contraindications

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▪ more doctors are prescribing -
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"Chlorothiazide was given to 16 patients for a total of 295 patient-treatment days." "Chlorothiazide is a safe, oral diuretic with a clinical effect equal to or greater than a parenteral mercurial." Harvey, S. D. and DeGraff, A. C.: N. Y. State J. Med., **59**:1769, (May 1) 1959.



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". . . our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, **3**:199, (Feb.) 1959.



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"Chlorothiazide is an excellent agent for relief of swelling and breast soreness associated with the premenstrual tension syndrome, since all patients [50] with these complaints were completely relieved." Keyes, J. W. and Berlacher, F. J.: J.A.M.A., **169**:109, (Jan. 10) 1959.

DOSAGE: Edema—One or two 500 mg. tablets DIURIL once or twice a day. Hypertension—One 250 mg. tablet DIURIL twice a day to one 500 mg. tablet DIURIL three times a day.

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in edema of pregnancy

e hundred patients were treated with chlorothiazide." "In the presence of ically detectable edema, the agent was versally effective." "Chlorothiazide is present the most effective oral diuretic pregnancy." Landesman, R., Ollstein, N. and Quinton, E. J.: N. Y. State J. ., **59**:66, (Jan. 1) 1959.



in cirrhosis with ascites

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., **103**:415, (March) 1959.



in renal edema

"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., **103**:369, (March) 1959.

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1. Case reports on file, Wyeth Laboratories. 2. Parks, R.V., and Moessner, G.F.: Dual Approach to Patient Care, Scientific Exhibit, A.A.G.P., April, 1959.

"Nausea and vomiting? Not any more!"





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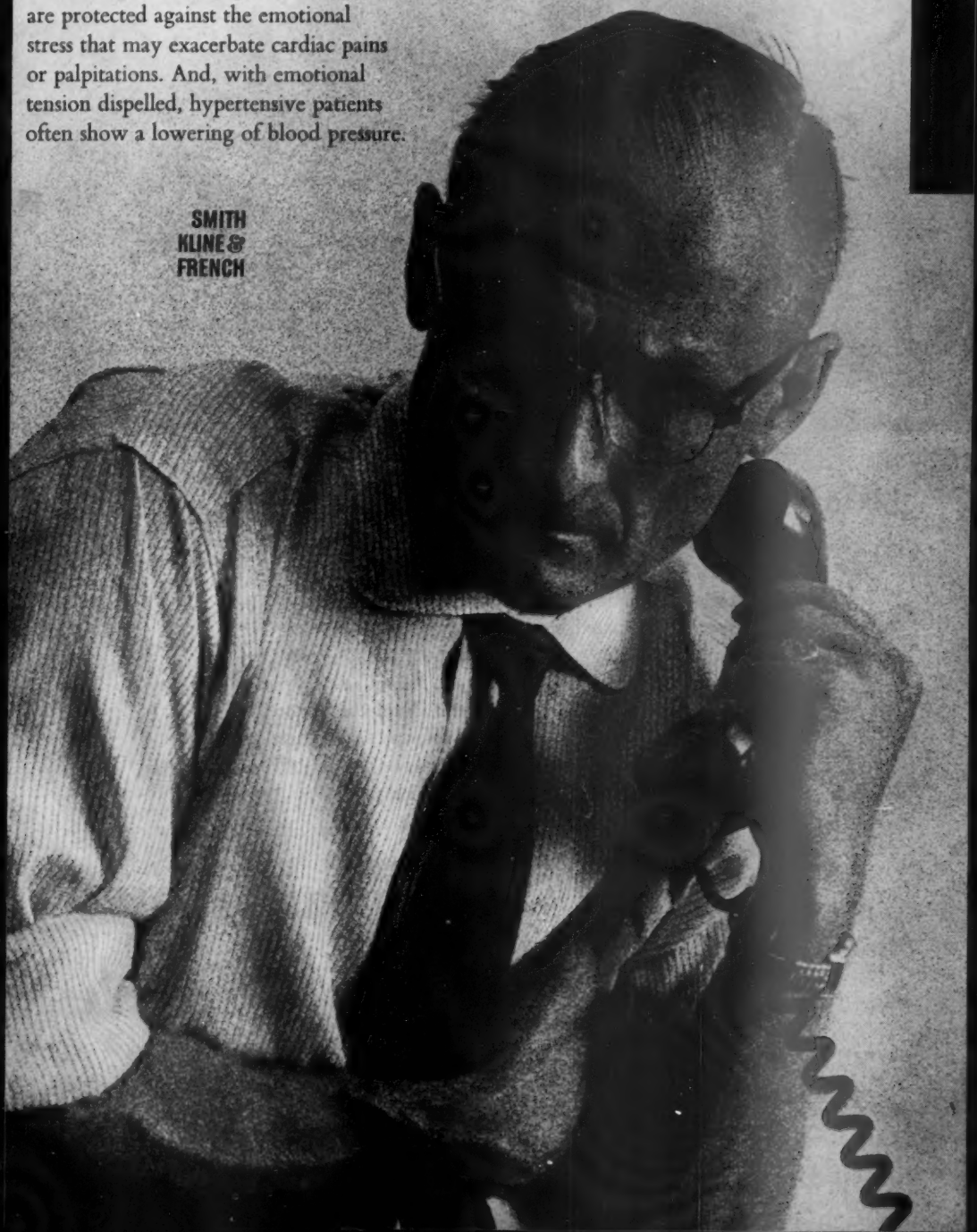
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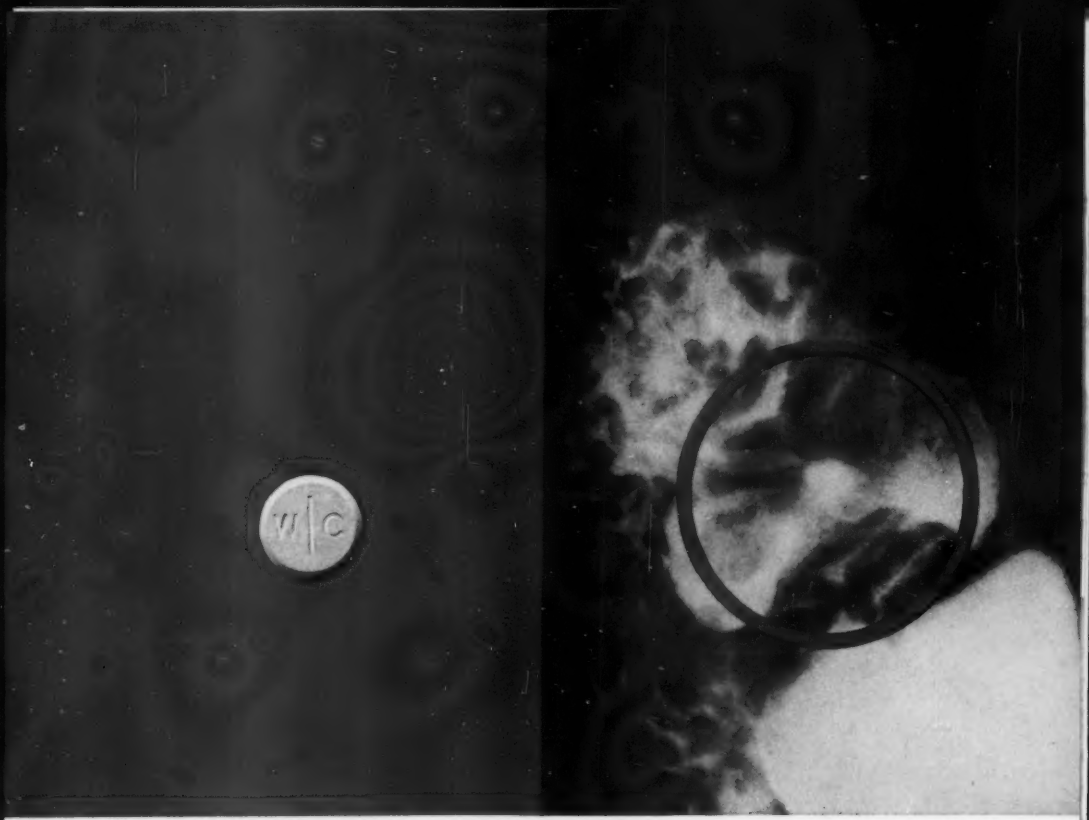
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1. Wharton, G. K. and Osmon, K. L.; Antacid Therapy in Peptic Ulcer: Clin. Med. V:5 (May, 1958).
2. McHardy, G. et al; Exhibit, So. Med. Assn., New Orleans, La., Nov. 1959.

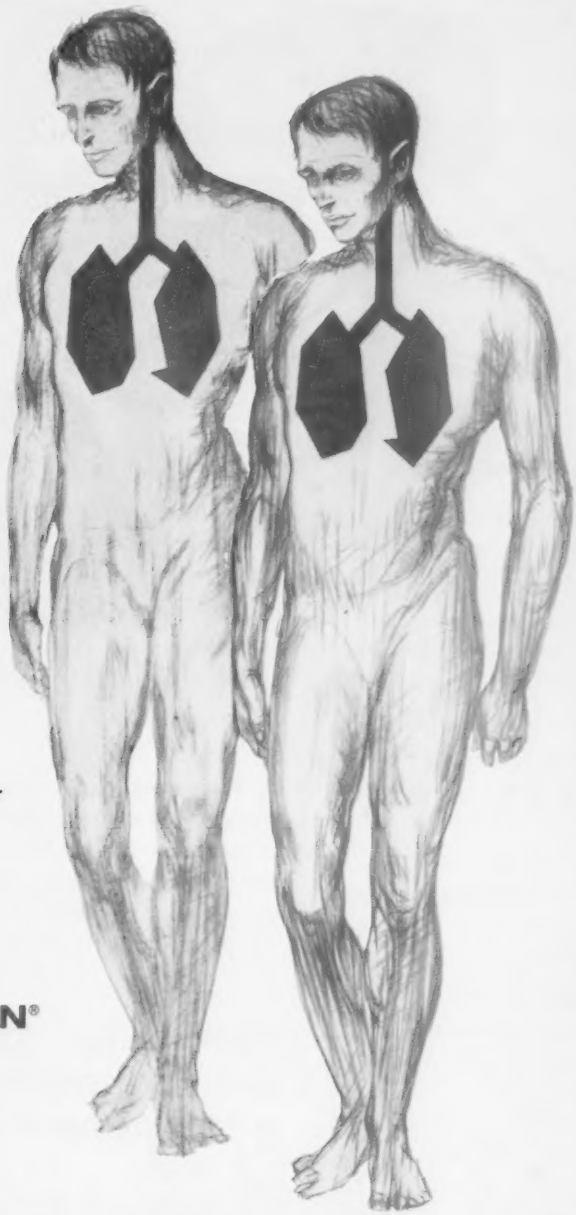
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References:

W. J. Kolff, "Acute Renal Failure: Causes and Treatment," The Medical Clinics of North America, *30*:1052 (July 1955).

Peter Forsham, "Symposium on Adrenal Corticoid Therapy," Metabolism, *7*:19 (Jan. 1958).

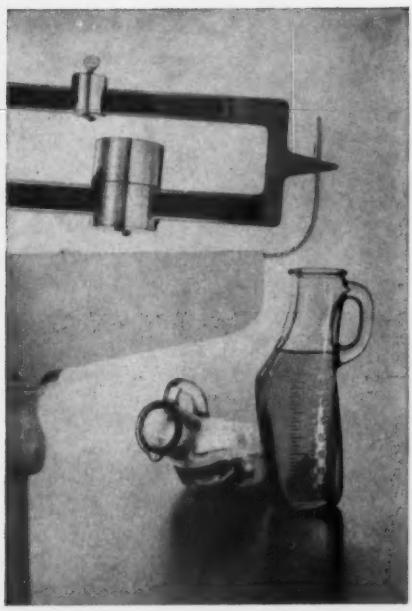
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brand of pentaerythritol tetranitrate

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Supplied: Tablets, scored, 20 and 40 mg., vials of 100.

Complete literature supplied

References: 1. Dunsmore, R.A., et al.: [illegible] Sc. Exp. Med. (Oct.) 1955. 2. Sheridan, P., et al.: Univ. Michigan M. Bull. 24:409 (Oct.) 1958. 3. [illegible] for publication. 4. [illegible] Submitted for publication.

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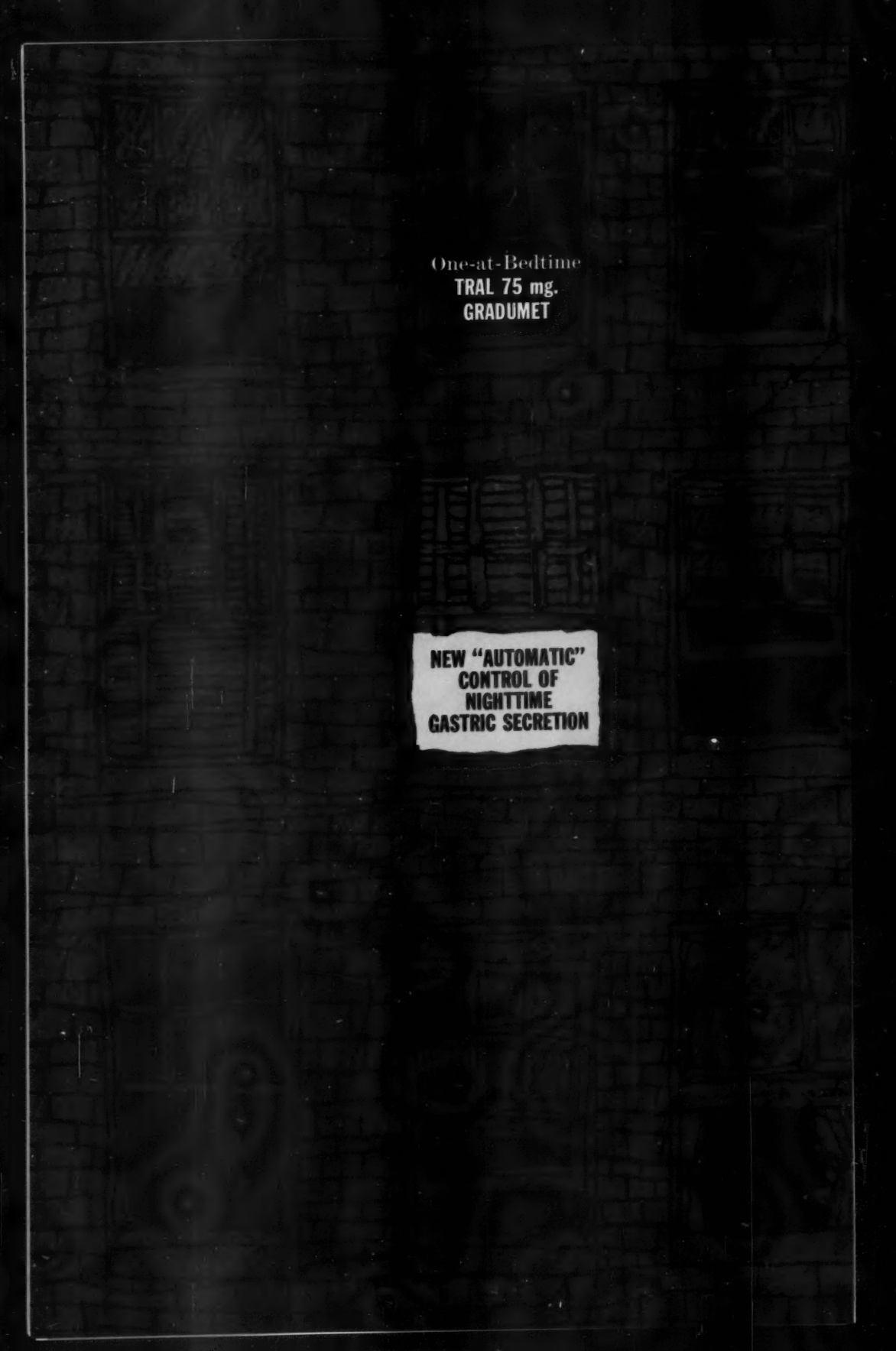
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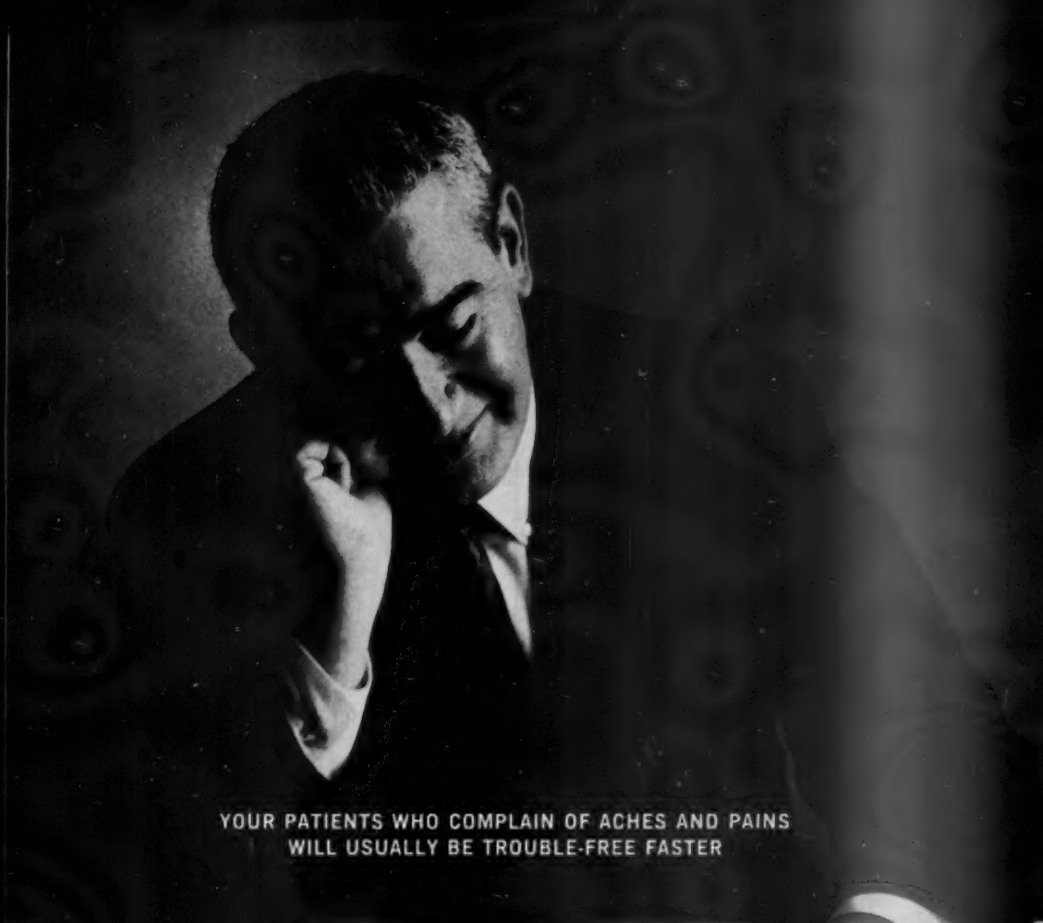




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* Muir, A.: Aspirin and Gastric Damage, Scientific Exhibit, A.M.A. Convention, Atlantic City, N. J., June 8-12, 1959.

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RESULTS IN 366 PATIENTS WITH STOMACH ULCERS

DIAGNOSIS	TOTAL	MARKED IMPROVEMENT WITH X-RAY GAINS	MARKED IMPROVEMENT	SLIGHT IMPROVEMENT	NO IMPROVEMENT
PEPTIC	50	10	29	9	2
GASTRIC	56	11	33	10	2
DUODENAL	256	39	175	33	9
PYLORIC	4	—	1	2	1
TOTAL	366	60	238	54	14
		16%	65%	15%	4%

Summary of investigators' reports.

81% MARKED IMPROVEMENT REPORTED

proven relief of pain, spasm and nervous tension without the side effects of belladonna, bromides or barbiturates

INDICATIONS—

duodenal and gastric ulcer
gastritis
colitis
spastic and irritable colon
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functional diarrhea
G. I. symptoms of anxiety states

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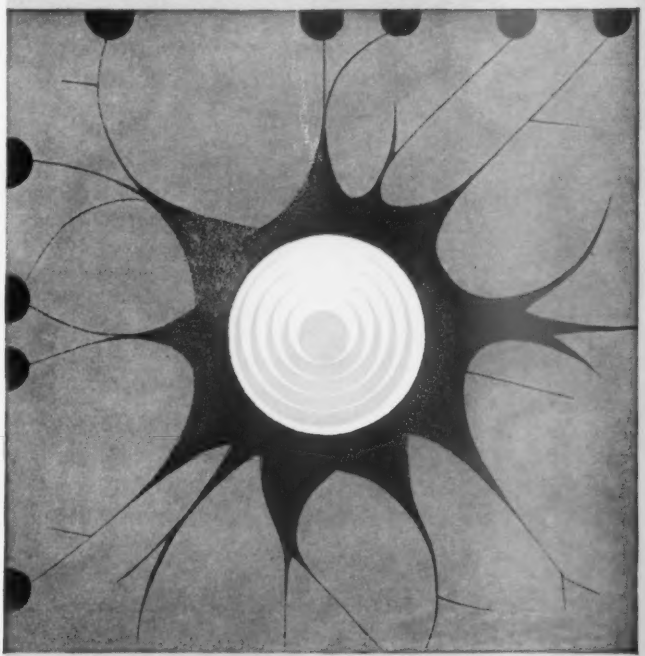
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References: 1. Ayd, F. J., Jr.: Bull. School Med., Univ. Maryland *44*:29, 1959. 2. Azima, H., and Vispo, R. H.: A.M.A. Arch. Neurol. & Psychiat. *81*:658, 1959. 3. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. *3*:155, 1958. 4. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. *4*:38, 1959. 5. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M.A.J. *80*:540, 1959. 6. Straker, M.: Canad. M.A.J. *80*:546, 1959. 7. Strauss, H.: New York J. Med. *59*:2906, 1959.

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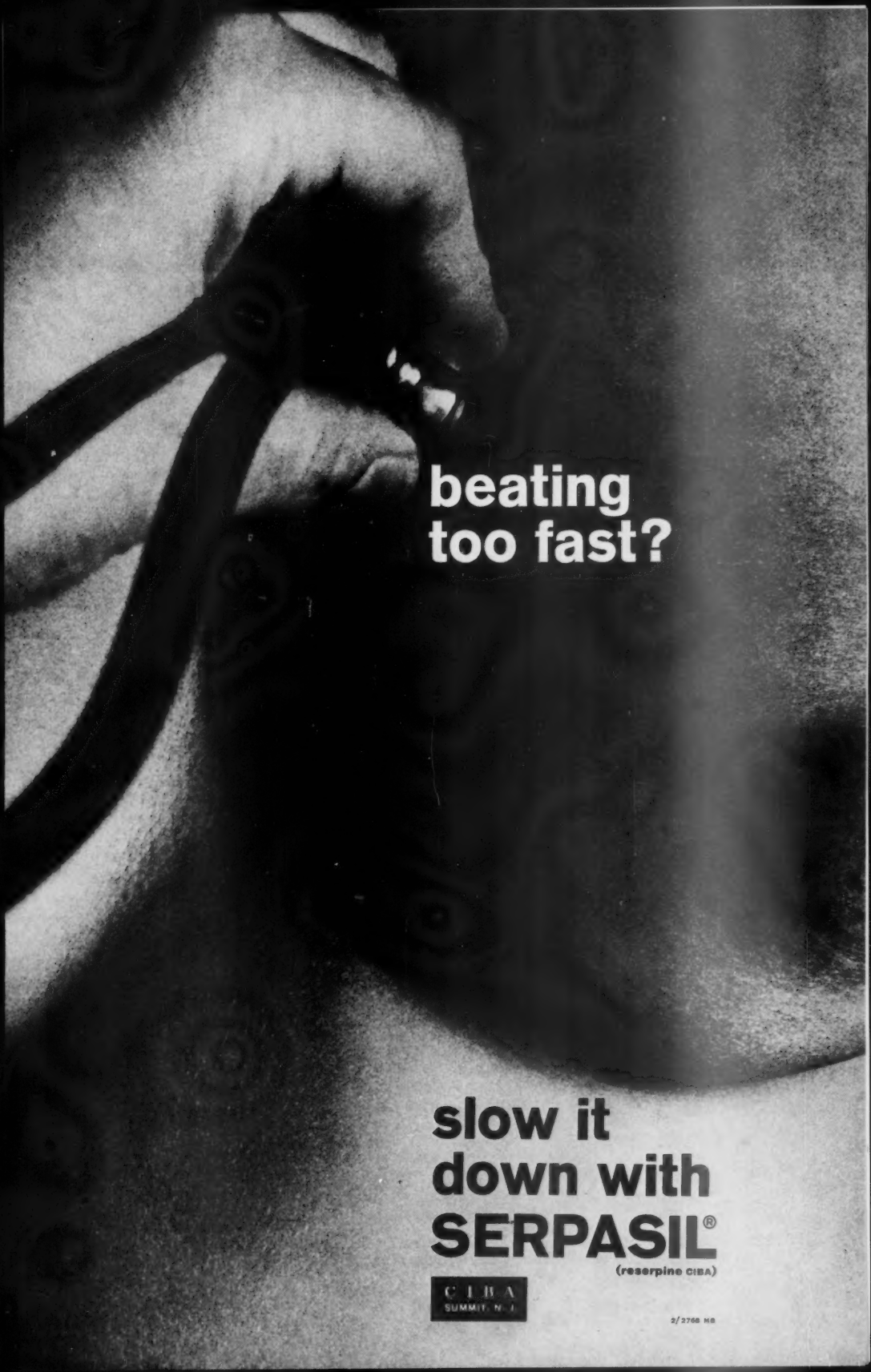


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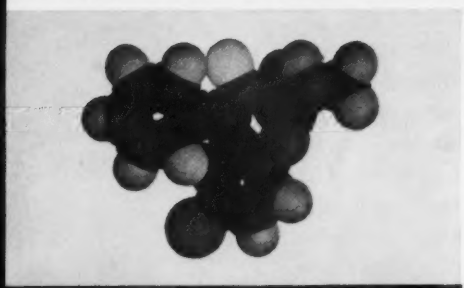
in a class by itself—clinically

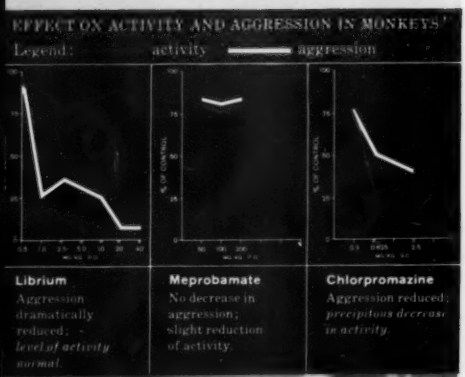
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Published reports on Librium: 1. G. A. Constant, *Dis. Nerv. System*, 21:(Suppl.), 37, 1960. 2. T. H. Harris, *ibid.*, p. 3. 3. L. O. Randall, *ibid.*, p. 7. 4. H. A. Bowes, *ibid.*, p. 20. 5. J. M. Tobin, I. F. Bird and D. E. Boyle, *ibid.*, p. 11. 6. J. Kinross-Wright, I. M. Cohen and J. A. Knight, *ibid.*, p. 23. 7. H. H. Farb, *ibid.*, p. 27. 8. C. Breitner, *ibid.*, p. 31. 9. I. M. Cohen, *ibid.*, p. 35. 10. L. J. Thomas, *ibid.*, p. 40. 11. R. C. V. Robinson, *ibid.*, p. 43. 12. S. C. Kaim and I. N. Rosenstein, *ibid.*, p. 46. 13. H. E. Ticktin and J. D. Schultz, *ibid.*, p. 49. 14. J. N. Sussex, *ibid.*, p. 53. 15. I. N. Rosenstein, *ibid.*, p. 57. 16. I. N. Rosenstein and C. Silverblatt, to be published.

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from anxiety and tension, whether presenting symptomatology or associated with organic or functional disorders.

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from the frustrations of prolonged, inconclusive treatment and to render the patient more amenable to therapy.

uses of Librium

in the office patient, troubled by anxiety and tension, and by the irritability, fatigue and nervous insomnia associated with tension states

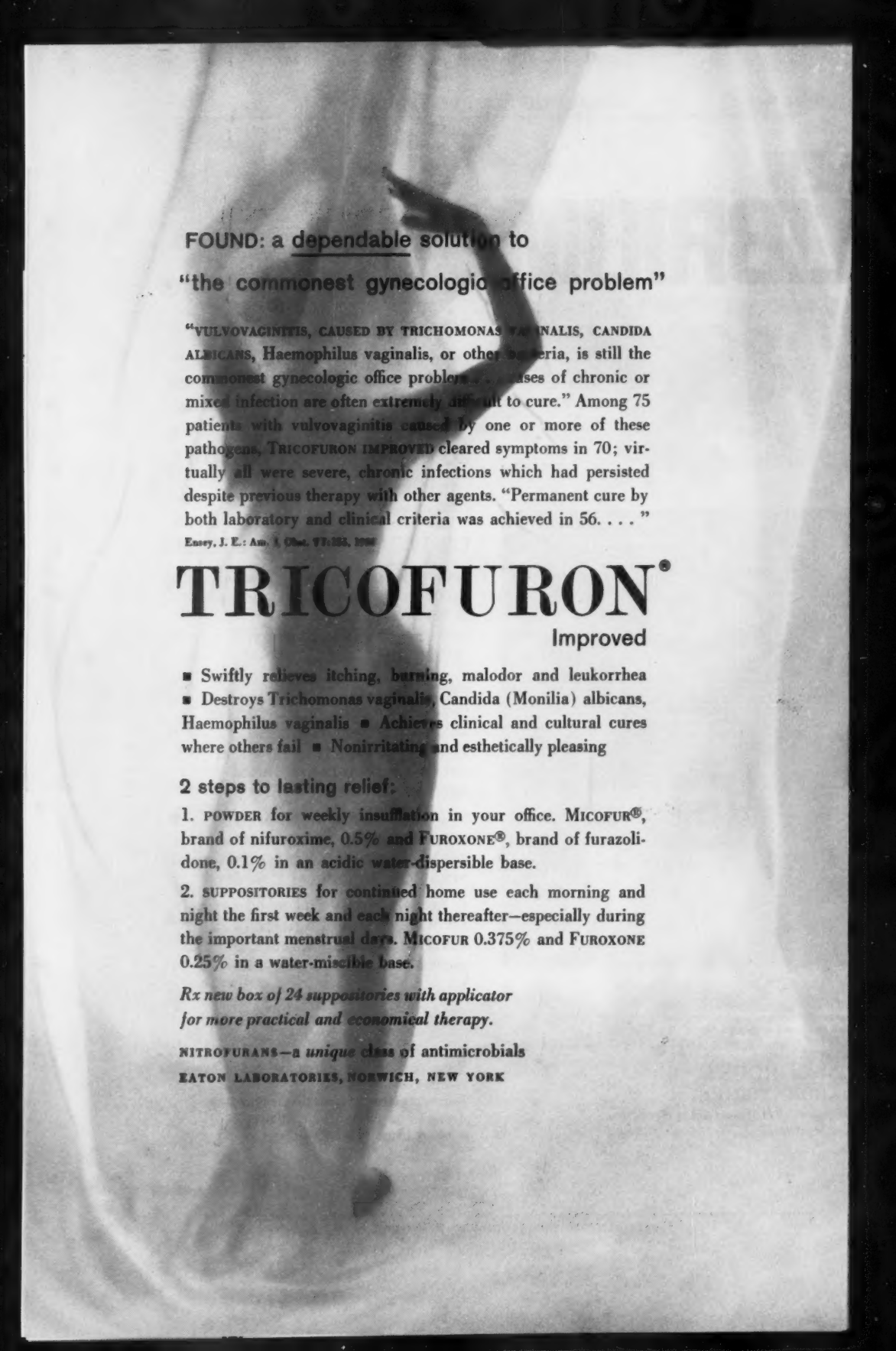
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Emery, J. E.: Am. J. Obst. 77:153, 1959

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in anxiety-tension states . . .

Butisol safely, smoothly filters out the undesirable effects of everyday anxiety and tension—but leaves initiative and responsibility intact to meet the problems and complexities of daily life.

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most commonly encountered in:

psychosomatic disorders
chronic diseases
other organic illnesses

most commonly expressed by:

nervousness
anorexia
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sadness
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irritability
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a true antidepressant which relieves the depression-induced anxiety by alleviating the depression itself

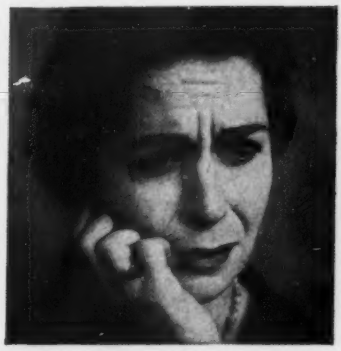
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brand of phenelzine dihydrogen sulfate

a true antidepressant—*not* a tranquilizer

the common problem basically unresponsive to tranquilizers

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On Nardil "the majority of her anxiety symptoms had disappeared. Later she remarked that she was 100% better....There has been no return of former complaints."*

*Hobbs, L. F.: *Virginia Med. Monthly 86*:692, 1959.



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**Sainz, A.: *Dis. Nerv. System 20*:537, 1959.

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nswers best the question of how treat patients with allergic dermatoses.

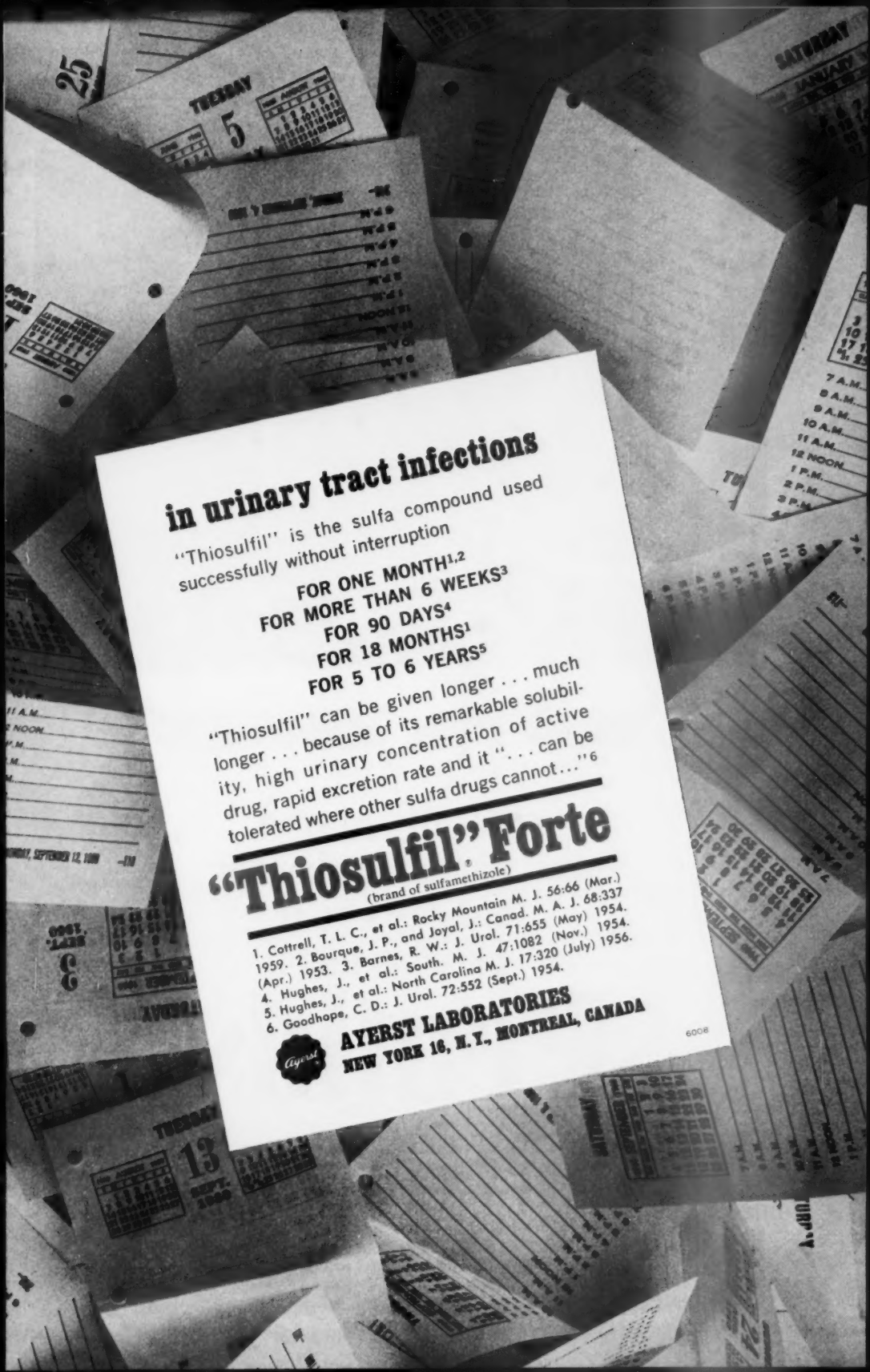
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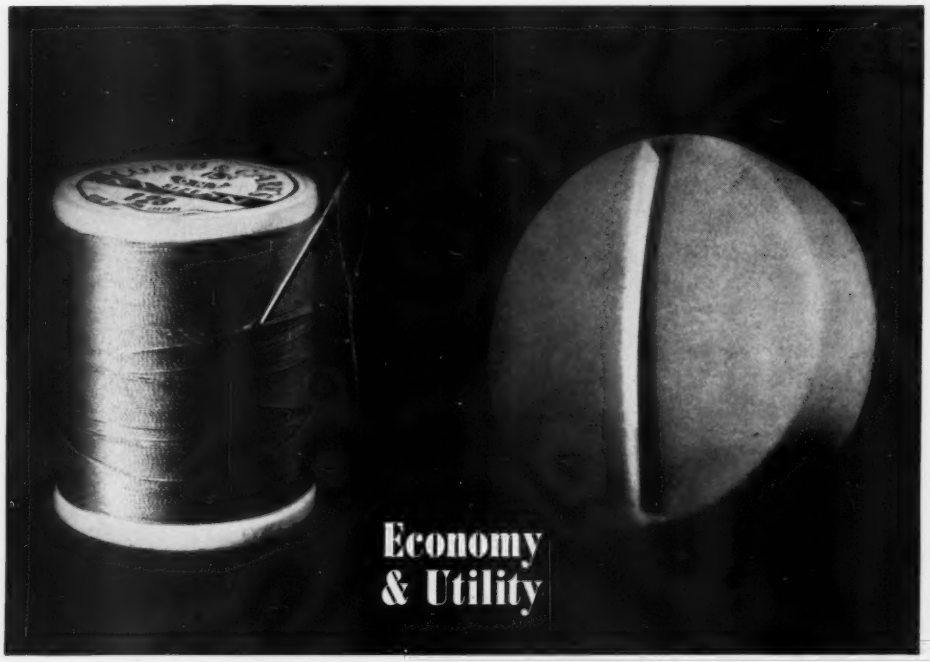
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7
JAN. 1960
MONDAY
5
SEPT. 1960
7 A.M.
8 A.M.
9 A.M.
10 A.M.
11 A.M.
12 NOON
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MONDAY, SEPTEMBER 5, 1960
MONDAY
JANUARY 1960
FRIDAY
JULY 1960
22
JULY 1960
20
AUG. 1960
TUESDAY
9 A.M.
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rapid, reliable control
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THE DIGITALIZED CARDIAC WHO IS LOSING TOO MUCH K

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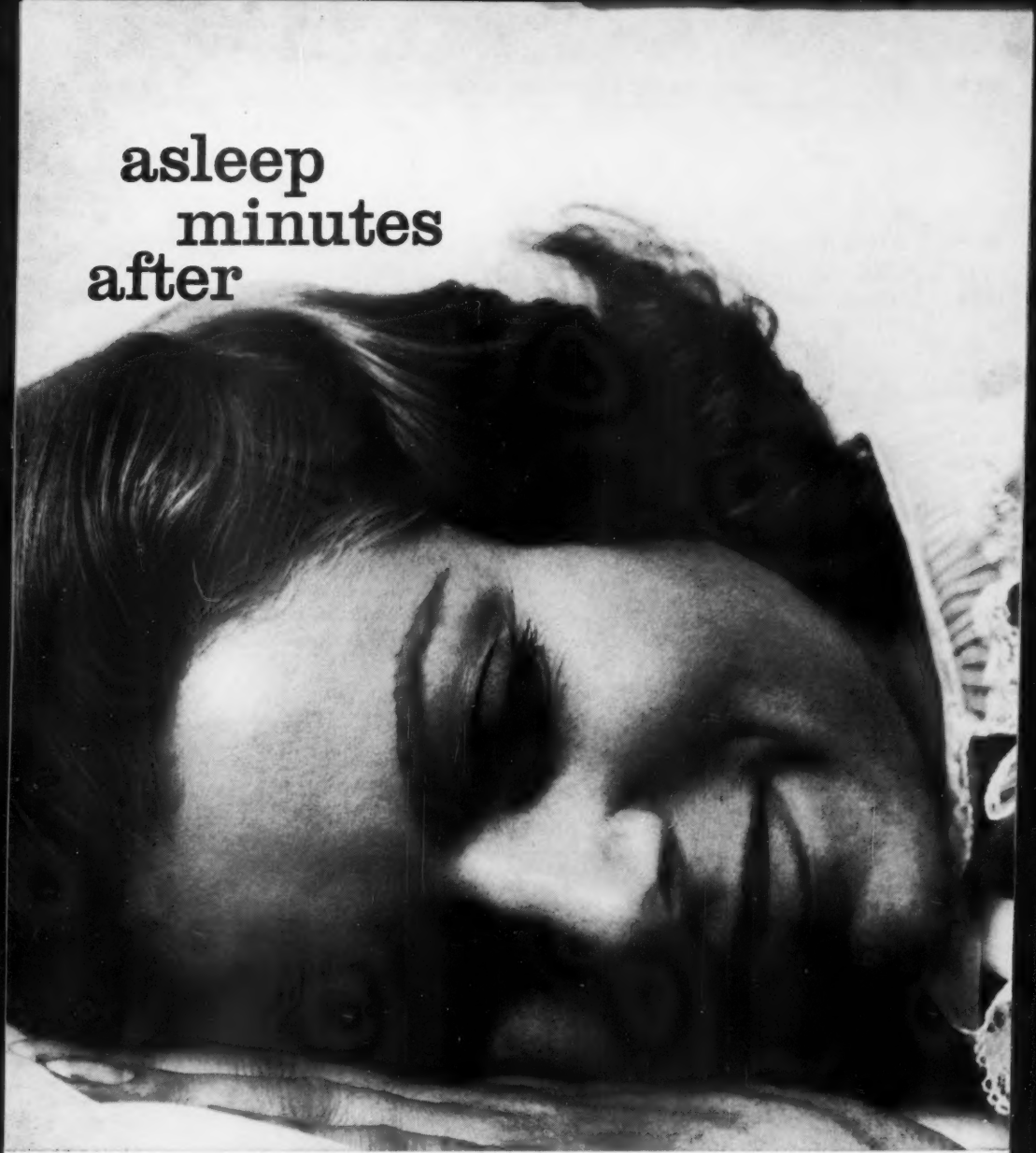
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Bibliography: (1) Paul, O., *et al.:* A.M.A. Arch. Path. *64*:363, 1957. (2) Council on Drugs: J.A.M.A. *172*:240 (Jan. 16) 1960. (3) Pitts, R. F., *et al:* J. Pharmacol. & Exper. Therap. *123*:89, 1958. (4) Wilkins, R. W.: J.A.M.A. *167*:801 (June 14) 1958. (5) Healey, L. A.; Magid, G. J., and Decker, J. L.: New England J. Med. *261*:1358 (Dec. 31) 1959. (6) Questions and Answers: J.A.M.A. *172*:115 (Jan. 2) 1960. (7) Heineman, H. O.; DeMartini, F. E., and Laragh, J. H.: Am. J. Med. *26*:853, 1959.

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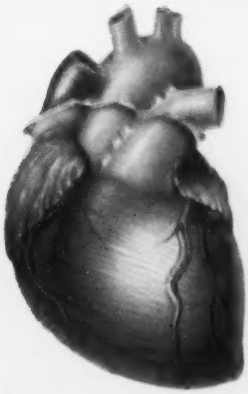
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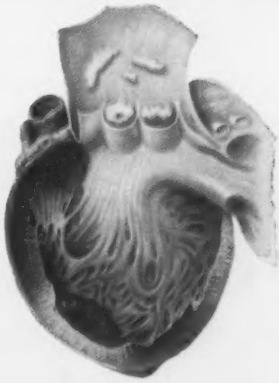
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... the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



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Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

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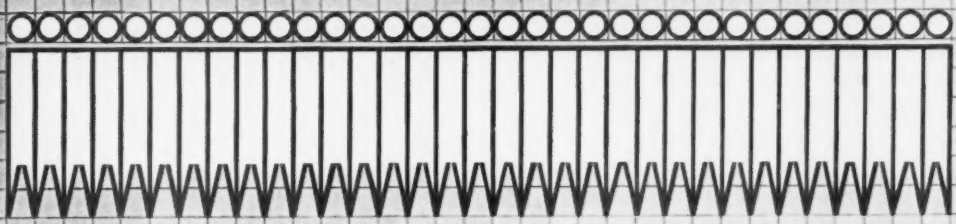
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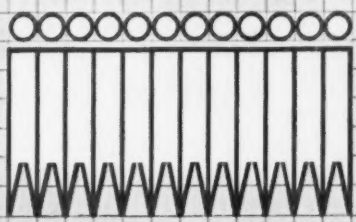
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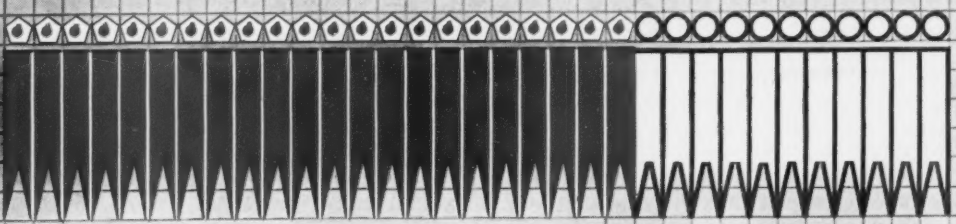
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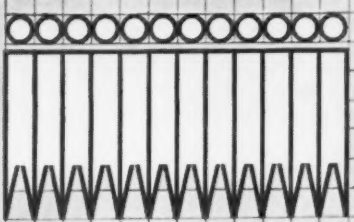


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THE COURSE OF MITRAL STENOSIS WITHOUT SURGERY: TEN- AND TWENTY-YEAR PERSPECTIVES *

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A DECADE has elapsed since the introduction of a successful operation for mitral stenosis, and survival curves for this 10-year period are now available. Surprisingly little factual information is at hand, however, as to the comparable course in the presurgical era of those patients treated medically. To supplement the existing data in this respect, and to establish a helpful base line for future reference, we are reporting herewith 10- and 20-year perspectives on the course of mitral stenosis in patients studied in the cardiac clinics and private practice of the three senior authors at the Massachusetts General Hospital and the House of the Good Samaritan in Boston.

The material consists of 250 patients with mitral stenosis who were followed until death or for a minimal period of 10 years; of this group, 115 patients were followed for 20 years. Initial examination between 1925 and 1947 revealed in all instances the classic auscultatory findings of isolated mitral stenosis: accentuated apical first sound, opening snap and apical diastolic murmur. One hundred twenty-eight patients, or over half, had these signs only; another 53, in addition, had a soft apical systolic murmur, and still another 52 patients had a soft blowing early diastolic murmur at the

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left sternal border; 17 had both of these murmurs in addition to the classic signs of mitral stenosis.

There were 194 females and 56 males. They were divided into the accepted grades of severity at the time of the first examination, as follows: (1) auscultatory signs of mitral stenosis without symptoms and with normal rhythm, 52%; (2) mild symptoms with normal rhythm, or atrial fibrillation, with or without symptoms, 37%; (3) moderate to moderately severe symptoms, or a major complication, 10%; (4) chronic heart failure, 1%. Eighty-three patients were under 20 years of age, 55 were in their twenties,

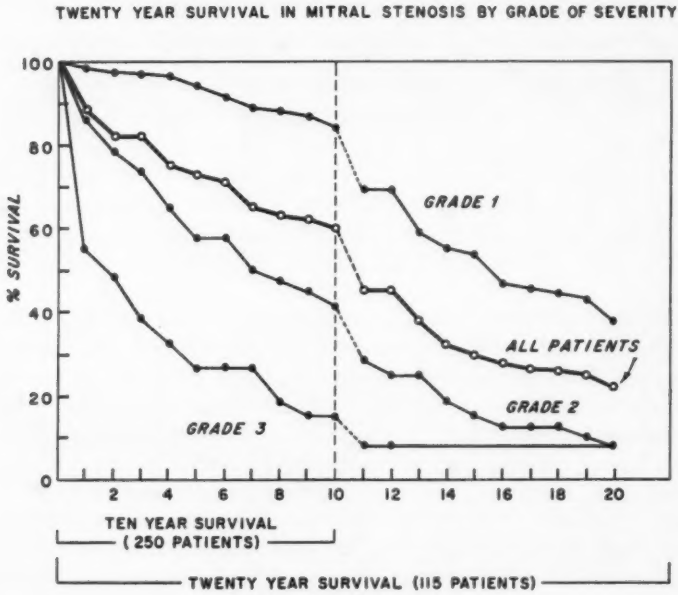


FIG. 1.

44 in their thirties, 35 in their forties, and 33 were over 50. The predominance of young and asymptomatic patients is due to the large contribution of 108 cases from the House of the Good Samaritan series of Bland and Jones.[1]

Fifty-nine per cent of the total number gave a history of rheumatic fever, including all of the 108 from the House of the Good Samaritan. There was a history of chorea, with or without other manifestations of rheumatic fever, in 37% of the women and 16% of the men.

TEN-YEAR FOLLOW-UP OF 250 PATIENTS

A. *Survival:* Figure 1 indicates the survival curves following the first examination for the series as a whole and for each of the four groups, graded

for severity. Except for the asymptomatic patients (Grade 1), each group had its highest mortality in the first five years. Of the entire series, 61% lived 10 years; in Grade 1, 84% lived 10 years; in Grade 2, 42%, and in Grade 3, 15%. Men and women lived equally long. Older patients naturally had a shorter survival time.

B. *Change in 10 Years:* At the conclusion of 10 years, two fifths of these patients remained in the same grade of severity as before, two fifths of them had died, and one fifth had progressed to a category of greater severity. A few patients with pulmonary edema remained symptom-free following this acute episode.

At end of first 10 years	Same	Worse	Dead
Grade 1	59%	25%	16%
Grade 2	21%	21%	58%
Grade 3	4%	11%	85%
Grade 4	0	0	100%
All patients	39%	22%	39%

C. *Cause of Death:* The cause of death was known in 110 cases (table 1). The majority of these patients (67) died of progressive heart failure, sometimes with complicating pulmonary emboli. Arterial embolism was the primary cause in 21 instances (cerebral in 17), and pulmonary embolism, single or multiple, in 10. Five patients succumbed to subacute bacterial endocarditis before the antibiotic era. The remainder died of unrelated disease. There was little difference between men and women in the cause of death except in the 21 deaths from arterial emboli, 19 of which occurred in women.

TABLE 1

Ten-Year Fatalities in Mitral Stenosis
(110 Cases)

	Cases	Per Cent
Congestive failure	67	61
Systemic embolus	21	19
Pulmonary embolus	10	9.0
Bacterial endocarditis	5	4.5
Unrelated disease	7	6.3

D. *Major Symptoms and Complications:* Table 2 summarizes the incidence of major symptoms and complications prior to the first examination and for the ensuing 10-year period.

(1) *Dyspnea:* Half of the patients had experienced shortness of breath when first seen, and two thirds developed this symptom during the 10 years. For a given degree of valvular disease, older patients were more dyspneic, reflecting in part the influence of emphysema and associated coronary and hypertensive heart disease. Patients with fibrillation had more dyspnea than did those with comparable valvular disease but normal rhythm.

Acute pulmonary edema was usually associated with advanced disease and symptoms, although several pregnant women, otherwise asymptomatic, developed it, as did a few other patients during unusual physical effort.

(2) *Atrial fibrillation:* When first seen, one fifth of all patients had established atrial fibrillation. In addition, 9% had paroxysmal fibrillation, and 1%, atrial tachycardia. At the end of 10 years, one third of the series had established fibrillation.

Of the 50 patients with established fibrillation at the first visit, 37 were women and 13 were men. They were predominantly in the older age groups, 38 being over 40 years of age. Thirty were considered to have disease of Grade 2 severity, 18 of Grade 3 severity, and two of Grade 4 severity. The survival of these patients is comparable to that of all patients of similar age and grade of severity: one-half were alive after four years, and approximately one quarter at the end of 10 years. As would be expected, the more severely afflicted patients had more marked symptoms of congestive failure and a more striking incidence of pulmonary embolism (10%) and arterial em-

TABLE 2

Major Symptoms and Complications of Mitral Stenosis
250 Patients Followed for 10 Years

	Prior to First Visit	Cumulative After 10 Years
Dyspnea	47%	65%
Pulmonary edema	8%	15%
Right-sided failure	9%	24%
Paroxysmal fibrillation	9%	12%
Chronic fibrillation	21%	33%
Hemoptysis	9%	9%
Arterial embolism	6%	16%
Pulmonary embolism	2%	8%
Bacterial endocarditis	1%	2%
Hypertension	6%	6%

bolism (18%). All of the patients who had had pulmonary embolism and 15 of the 17 who had had arterial embolism prior to the first visit were fibrillating. During the first 10 years, 36 of the 50 patients with established fibrillation died. Embolic episodes continued to be frequent: 10% had clinically obvious pulmonary embolism during the 10 years, and 26% had arterial embolism.

In the 10-year period an additional 35 patients developed atrial fibrillation, bringing the total to one third of the entire series. All of the 30 patients who experienced arterial emboli and 14 of the 16 with recognized pulmonary emboli during the follow-up period were fibrillating at the time of the event. One fibrillating patient developed subacute bacterial endocarditis.

(3) *Arterial embolism:* Arterial embolism had occurred in 6% of all patients prior to the first visit, and was a major cause of disability and death in the follow-up period. Twelve per cent of the series had emboli during the 10 year period, making a total of 16% of all patients by the end of the tenth year.

Among those who had emboli before they were first examined, 17 patients had had 21 separate embolic episodes, and of this group all but one, or 16 patients, were women. Sixteen of these episodes had involved the cerebral vessels, two the renal, two the splenic, and one the leg vessels.

In the 10-year follow-up period, 30 patients had 48 embolic attacks. Twenty-three emboli were to the brain, 12 to the iliac or leg vessels, eight to the kidneys, two to the arm, two to the spleen, and one to the mesenteric vessels. Twenty-six of the 30 patients were women. They experienced 40 of the 48 embolisms. In addition to the clinically recognized emboli, a few patients showed renal emboli at autopsy. (All of these had had other recognized embolic episodes.)

Almost all of the emboli occurred in patients who had atrial fibrillation at the time of the event. Of the 250 patients in this series, 47 had had one or more arterial emboli at some time in their course. Forty-three were women, and four were men. Of these 47, 12 died as a direct result of the embolism, which was cerebral in nine instances. Nineteen of those who recovered had no further emboli during the period of observation. In the remaining 16 a second embolic episode occurred, occasioning seven deaths. Of these subsequent emboli, half occurred within a year following the first episode. Three patients suffered three or more separate embolic episodes, and one patient had at least eight in a period of four years.

(4) *Bacterial endocarditis:* One patient had bacterial endocarditis when first seen, and four patients developed it during the 10 years (2% incidence). The ages of these five patients were 16, 21, 27, 35 and 55, respectively. Four were women. All but the oldest had normal rhythm. All five patients were seen before the era of penicillin and succumbed to the infection.

(5) *Hypertension:* Associated hypertension (blood pressure over 170 mm. systolic and 100 mm. diastolic) was noted in 6% of the 250 cases, the percentage remaining constant during the 10 years. The incidence was the same in men and women, and increased with age.

Mean systolic and diastolic pressures for the various age groups were as follows:

Under 20	110/70
Twenties	115/75
Thirties	120/80
Forties	135/90
Fifty and over	145/90

Twenty-Year Follow-up of 115 Patients

A. *Survival:* This portion of the original 250 patients represented somewhat older and sicker patients, because those from the House of the Good Samaritan series were younger and had less advanced disease. They have not as yet had their mitral stenosis 20 years, and are therefore not included. Of these 115 20-year patients, 43% had originally been classified as Grade 1

severity, 45% as Grade 2, and 12% as Grade 3, in contrast to the original 250 patients, with 52%, 37% and 10% in these respective grades. In this somewhat more severely afflicted group, the survival curve dropped more rapidly. Figure 1 shows 45% surviving in the eleventh year, 30% in the fifteenth year, and 21% at the end of 20 years. Of those classified Grade 1, 40% lived for 20 years, while in Grades 2 and 3 only 8% survived this long.

B. *Change in 20 Years:* At the conclusion of 20 years, 13% of these patients had not changed in grade of severity:

	Same	Worse	Dead
Grade 1	24%	14%	62%
Grade 2	4%	4%	92%
Grade 3	8%	0	92%
All patients	13%	8%	79%

C. *Major Symptoms and Complications:* Table 3 summarizes the major symptoms and complications of the patients in the 20-year group. The incidence of dyspnea is quite similar to that in the 10-year period, but pulmonary edema and right-sided failure developed more frequently. Arterial embolism continued to be an important feature, occurring almost exclusively in women. At the end of 20 years, arterial embolism had occurred at some time in 26% of these 115 patients.

Comparison with Other Series of Medically Treated Patients

In 1933 Grant [2] reported on the course of mitral stenosis in 238 males from the British armed services followed for 10 years after its discovery in World War I. Although these patients were exclusively male, they were

Table 3
Major Symptoms and Complications of Mitral Stenosis
115 Patients Followed for 20 Years

	Prior to First Visit	Cumulative After 20 Years
Dyspnea	47%	69%
Pulmonary edema	8%	21%
Right-sided failure	9%	36%
Chronic fibrillation	21%	43%
Arterial embolism	6%	26%
Pulmonary embolism	2%	9%

similar in age and in severity of disease to those in the present series, and their survival data are also comparable (curve B, figure 2).

More recently, Olesen [3] has reviewed 271 patients with isolated mitral stenosis. Although the author estimates that about one quarter of this group may also have had significant mitral insufficiency, the predominant lesion was believed to be mitral stenosis. They were followed for varying periods of time, but a uniform survival curve covering 10 years was constructed for them by an indirect method (curve D, figure 2). In general,

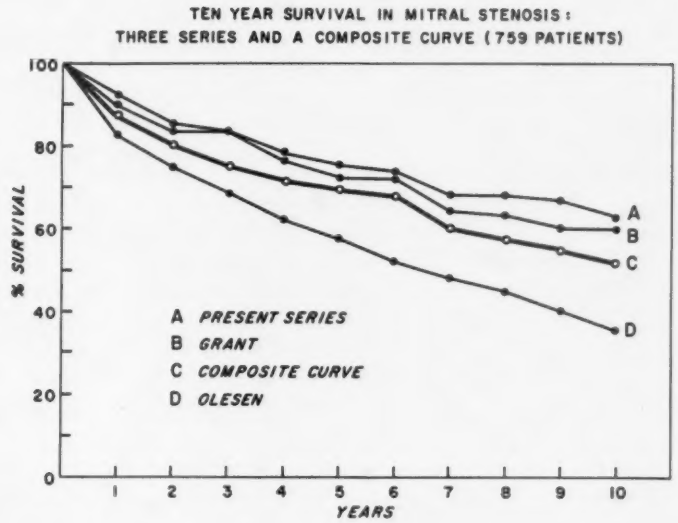


FIG. 2.

both age and disease were more advanced in this group than in our series, and the curve reflects this, with a 10-year survival of only 35%.

A composite survival curve of the 759 patients from the three series for a 10-year period of slightly over 50% is shown in figure 2 (curve C).

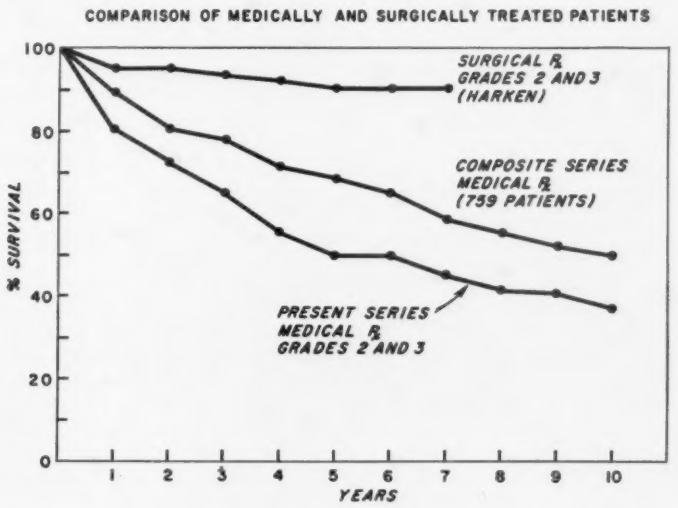


FIG. 3.

Comparison with Surgically Treated Series

The survival curves available for seven years of the surgically treated series of Harken et al.[4] are contrasted in figure 3 with the curves of comparable patients treated medically from our series, and with the composite curve of the three series of medically treated patients. Direct comparison must be tempered by the fact that the surgical patients were followed medically for some time prior to operation, as well as by the fact that the two groups were not contemporary. Nevertheless, to date the sustained benefits of mitral valvulotomy are evident from this comparison, although it is probable that medically treated patients with mitral stenosis live longer now than they did 10 and 20 years ago.

Summary

Two hundred fifty patients with mitral stenosis have been followed for 10 years or to death, and 115 of these have been followed for 20 years. The incidence and the significance in terms of longevity, of age, of severity of symptoms, and of such complications as atrial fibrillation, embolism and congestive failure are discussed. In 10 years, 40% died and 40% remained unchanged. In 20 years, 80% died and 13% remained unchanged.

Survival curves for the surgically treated series of Harken et al. are contrasted with those of medically treated cases from our series and from those of Grant in England and Olesen in Denmark. It is evident from this comparison that the considerable early benefit from mitral valvulotomy has been sustained through the ensuing years.

Summario in Interlingua

Es reportate perspectivas de 10 e 20 annos pro le curso de stenosis mitral tractate medicalmente durante le era ante le introduction de un operation successose pro iste condition. Le casuistica consisteva de 250 patientes studiate al Hospital General de Massachusetts e al Casa del Bon Samaritano a Boston. Le gruppo total ha essite sub observation sequential durante 10 annos e 115 durante 20 annos. Es discutite e interpretate datos relative al longevitate e etate del patientes e al severitate de lor symptomas como etiam al incidentia de complicationes como fibrillation atrial, embolismo, e disfallimento congestive. In 10 annos, 40% moriva e 40% remaneva inalterate. In 20 annos, 80% moriva e 13% remaneva inalterate.

Fibrillation atrial esseva presente in 21% del casos al tempore del prime consulta, in 33% al fin de 10 annos, e in 43% al fin de 20 annos.

Embolismo habeva occurrite in 6% ante le prime consulta. Illo esseva un causa major de invaliditate e morte in le annos sequente, e 16% de omne le patientes habeva habite embolos al fin del decime anno e 26% al fin del vintesime anno.

Le causa de morte in le majoritate del 110 patientes qui moriva esseva progressive discompensation cardiac. Embolismo arterial esseva le causa primari de 21 mortes (cerebral in 17 casos), e embolismo pulmonar—simple o multiple—causava 10. Cinque patientes succumbeva a subacute endocarditis bacterial ante le advento del era de antibioticos. In le altere casos, le causa de morte esseva un morbo non affin.

Le curvas de superviventia del serie de Grant in Anglaterra (1933) e del serie

de Olesen in Danmark (1955) es comparate con illo del serie presente e ponite in contrasto con le serie del casos a tractamento chirurgic publicate per Harken et al. (1957). Le comparation rende apparente que le marcate beneficio immediate que resulta de valvulotomia mitral es sustenite in le curso del annos sequente.

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OBESITY AND DIABETES: A REËVALUATION*

By S. K. Fineberg, M.D., F.A.C.P., *New York, N. Y.*

The recent popular acceptance of oral hypoglycemic agents necessitates renewed and heavy emphasis on the primary importance of controlling obesity in the management of concomitant diabetes mellitus. The use of these agents in the treatment of maturity-onset, mild diabetes, at least, is now firmly entrenched and widespread. Although they have proved their worth, in selected cases, by providing control of the disease while freeing significant numbers of this type of diabetic patient from the pain and inconvenience of daily insulin injections, there is still foremost among the dangers inherent in this long sought-for modality an enormous potentiality for abuse.

Practical experience with large numbers of newly discovered diabetic patients has indicated that there is a natural repugnance toward self-injection, and many initial difficulties in mastering sterilization and the insulin injection technic. These and other objectionable aspects of insulin therapy have often served as strong inducements in obtaining eager coöperation, especially at first, with the weight-reducing diets indicated in the 80 to 90% of diabetics over the age of 30 who are overweight or obese.[1,2] Incentive, whatever its source, whether it arises spontaneously within the patient or is carefully implanted or fanned in him, is the major key to successful weight reduction. Oral hypoglycemic agents remove these very useful and practical, if artificial, incentives toward the simultaneous attainment of actual reversal of two serious diseases, diabetes *and* obesity. They also provide physicians with such an easily invoked and greatly demanded therapeutic tool that only those with real foresight and firm conviction will be able to restrict their use to the properly indicated cases.

Although diabetes is basically a disease of heredity in which carbohydrate metabolism is disturbed by a relative insufficiency of insulin, still, obesity is by far the most important of its precipitating and aggravating factors. Diabetes appears to be largely a penalty of obesity, and the greater the obesity, the more likely the penalty is to be inflicted. The association of obesity with diabetes is the rule rather than the exception, particularly in the late onset and milder form of the disease. As has been pointed out, it is just this type which is most likely to be controlled readily by the oral hypoglycemic agent. More significantly, amelioration and control of obesity-diabetes by the reduction of the patient's weight or the correction of his obesity will occur with greater frequency than by the use of hypoglycemic agents, and usually with an additional bonus of great benefit to his general health.

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It has long been known that many early, mild, obese diabetics, when successfully treated by diet to the point of restoring normal weight, no longer demonstrate any impairment of carbohydrate metabolism, even by carefully performed glucose tolerance tests.[3, 4] Less spectacular, but nonetheless desirable and beneficial, is the almost universal reduction in insulin requirement in the more severe diabetics and, quite commonly, the elimination of the need for insulin entirely (without the substitution of an oral medication!).[2, 5, 6] In a recent reappraisal of the effect of weight reduction on a group of 19 obese diabetics, all 19 (100%) demonstrated improvement of the glucose tolerance test after weight loss. Sixteen (84%), however, although they had attained normal tolerance on the standard glucose tolerance test, still showed an abnormal response to a cortisone-modified glucose tolerance test.[7] This latter test will detect the recently defined "prediabetic state," or potentially diabetic individual. It is performed by priming the subject with 100 to 125 mg. of cortisone orally in two doses, eight and one-half and two hours before a standard glucose tolerance test. Most remarkable was the finding that three (16%) of these known diabetics who were obese before treatment achieved a normal carbohydrate tolerance not only on the standard but also on the cortisone-glucose tolerance test. The first part of this demonstration, using only the response to a standard glucose tolerance test, of course, was reported by Newburgh and Conn more than 20 years ago.[8] It stands as a major contribution to the understanding and management of the obese diabetic patient.

Scientific proof of the value of weight reduction in the treatment of diabetes mellitus may be unquestionable and overwhelming, but it is of little use as an incentive, particularly to the poorly educated and underprivileged who attend the diabetic clinic of a large city institution. Once the newly discovered diabetic has become mentally adjusted and has developed some familiarity with his disease, he usually becomes as difficult to reduce as any case of obesity, perhaps more so if he is on insulin therapy. Despite lectures, pleas and threats, the records show that the majority do not reduce their weight significantly, although most may actually believe it is for their best interests to do so. It is apparent that a reasonably efficient means of instilling or creating new, sustained incentive for weight reduction, short of intensive psychotherapy, has not been forthcoming, and that even old incentives are presently being lost. Therefore, the use of an effective and essentially harmless substitute, not for insulin, but for psychologic reason and motivation, would be highly justified in this combined problem if such was available.

The anorexigenic agent as an artificial means of effecting coöperation with weight-reducing diets has been in general use for many years.[8, 9] The history of these substances in the treatment of obesity-diabetes also extends back some years.[6] At first their use in diabetes was criticized because of their supposed hyperglycemic action.[10] Later it was shown that this slight

hyperglycemic action, if any, mediated via the sympathetic nervous system (sympathomimetic), would be more than compensated for by the improvement in carbohydrate tolerance produced by the weight loss.[3, 4, 5, 6] Amphetamine and its derivatives were also restricted in the treatment of obesity with hypertension and cardiac disease because of their pressor and vasoconstrictor effects.[11, 12] Yet even the small, inconstant pressor effect of these compounds is usually overcome by the well known, almost constant blood pressure lowering effect of weight loss.

However, prejudices had been created by the raising of these questions and the differences of opinion regarding their answers. The knowledge that, in some cases at least, there could be some risk to the patient, however small, has inhibited the general use of these drugs in the treatment of obese diabetics, a group of patients in whom hypertensive cardiovascular disease is commonly found. This illogical attitude ignores the far greater threat which the accelerated vascular damage especially characteristic of poorly controlled diabetes and obesity poses to the individual. In addition, recent reports seem to indicate that in some latter-day versions of the anorexiant drug the pressor and vasoconstrictor effects have been reduced while the appetite suppressant effect has been retained. In these reports, blood pressures taken throughout the period of observation in a considerable number of cases reveal no significant elevations, and attest to the safety of the anorexiant even in hypertensive cardiac states.[13, 14, 15, 16] In view of this encouragement, it was decided to try one of these drugs under controlled conditions to determine, if possible, whether the results obtained would warrant its routine inclusion in the management of obese diabetics in a large clinic.

Material and Methods

Eighty patients were selected for this study, all of whom had been attending the Diabetic Clinic of Harlem Hospital for periods ranging from several months to many years. Only diabetic patients who were grossly obese as determined by inspection were included.

Alternate patients were given identical tablets labeled by code and containing either 25 mg. of phenmetrazine hydrochloride,* or a placebo without active medication. Neither the patients nor the dispensing physician knew which tablet was the placebo or which contained the active drug. In addition, as a third blind factor, the patients were not informed of the purpose or supposed action of the proffered medication. They were given no diets or dietary instructions of any kind. Supposedly all were on weight-losing, standard diabetic diets (total calories, 1,200 to 1,500), and had been for as long as they had been attending the diabetic clinic in an obese state. None of their records showed consistent, recent weight loss. Patients, when selected, were asked only if they would like to take tablets which would "help

* The phenmetrazine hydrochloride used in this study was supplied as Preludin by Geigy Pharmaceuticals, Ardsley, N. Y.

their diabetes." If they expressed willingness they were given one of the compounds and told to take one tablet one hour before each meal (30 to 40 minutes before breakfast). All who were taking insulin were cautioned to continue daily dosage until told otherwise. This was found to be necessary because there were patients in the same clinic who were receiving hypoglycemic agents. Many of the patients in this study believed that they also were getting a new insulin substitute. This impression was neither confirmed nor denied.

During the investigation, which lasted up to four months, patients were seen at approximately four-week intervals. The average individual observation period was about 10 weeks. At each visit they went through the customary routine for all diabetic patients in the clinic, and indirect inquiry was made for symptoms. Diet or appetite was not mentioned or discussed with the patients, even if they complained, as some did, about loss of appetite. Blood pressures were not taken, as it was felt that previous investigations

TABLE 1

Comparability of Groups

	Phenmetrazine	Placebo
Number of patients	29	25
Sex		
Male	1 (3.4%)	2 (8%)
Female	28 (96.6%)	23 (92%)
Age		
Range (years)	34–72	36–77
Mean age	53.0	52.2

None of the differences was statistically significant.

had established the safety and the lack of significant pressor effect of phenmetrazine in similar groups.[13, 14, 15, 16] Stress was placed on the taking of the medication at least one hour before lunch and dinner. All anorexigenic agents should be so taken that they are at least approaching the height of their effect when the patient sits down to eat. In this study, medication was given before breakfast because this has been standard procedure in similar investigations. However, it is felt that generally this is neither necessary nor desirable, as most individuals on calorically restricted diets actually need to develop the habit of eating more for breakfast than they do.

RESULTS

Twelve of the original group of 80 patients were not included in the final analysis because of poor coöperation, either in attendance or in taking the medication. Four of these were in the group taking phenmetrazine and eight in the placebo group. An additional nine patients had to be dropped because of the discovery or development of edema secondary to preëxisting cardiac or renal complications, and totally disruptive as far as weight studies of this nature are concerned. Five of these were in the phenmetrazine group and four in the placebo group.

TABLE 2

Diabetic Control at Start*

	Phenmetrazine		Placebo	
	No.	%	No.	%
Diet alone	8	27.6	5	20.0
Tolbutamide	1	3.4	2	8.0
Chlorpropamide	0		1	4.0
Insulin	20	69.0	17	68.0
Mean insulin dose	42.0		42.3	
Median insulin dose	35		35	

* The two groups were quite comparable with regard to the severity of their diabetes.

The investigation was not very far along before the veil began to lift from one portion of this "triple-blind" study. It seemed somewhat apparent from weight loss and occasional symptoms which tablet contained the active ingredient. In one group the medication had to be discontinued in five patients after periods varying from one to six weeks because of side-effects. The symptoms described were nausea, nervousness, inward tremor, palpitations,

TABLE 3

Summary of Data—Phenmetrazine Group

	Age-Sex	Start Treatment	End Treatment	Insulin Change	Weight Start, lbs.	Weight End, lbs.	Weeks Treated	Weight Change, lbs.
1	54 F	NPH 30	Diet	−30	176	172.5	5	−3.5
2	59 M	NPH 30	10	−20	244.75	235.75	10	−9
3	34 F	NPH 75	70	−5	269	266.5	12	−2.5
4	37 F	NPH 55	50	−5	208	182.25	11	−25.75
5	59 F	Diet	Diet		337	326.5	8	−10.5
6	58 F	Diet	Diet		165	162.5	4	−2.5
7	64 F	NPH 20	15	−5	232	225.5	4	−6.5
8	39 F	Diet	Diet		264.75	250	10	−14.75
9	54 F	NPH 30	Diet	−30	186	170	11	−16
10	59 F	Diet	Diet		188	181	8	−7
11	72 F	NPH 45	25	−20	187	181.25	8	−5.75
12	68 F	NPH 40	10	−30	169	165.25	10	−3.75
13	52 F	Diet	Diet		217.25	207.25	11	−10
14	59 F	NPH 40	20	−20	170.5	167	10	−3.5
15	58 F	NPH 25	15	−10	194.5	201.75	15	+7.25
16	37 F	NPH 15	10	−5	251.5	249	9	−2.5
17	39 F	NPH 80	55	−25	242.5	230.5	13	−12
18	40 F	NPH 45	45		200.75	203.5	5	+2.75
19	53 F	NPH 90	80	−10	189.5	178.25	9	−11.25
20	53 F	Tolbutamide			200	197	9	−3
21	36 F	NPH 40	Diet	−40	202.25	176	9	−26.25
22	50 F	Diet	Diet		185.75	180.25	9	−5.5
23	53 F	NPH 85	45	−40	231.5	230	9	−1.5
24	63 F	Diet	Diet		224	211	11	−13
25	54 F	Diet	Diet		212	207	18	−7
26	54 F	NPH 15	Diet	−15	173	168.5	13	−4.5
27	53 F	NPH 20	Diet	−20	225.75	219.75	13	−6
28	60 F	NPH 30	15	−15	230	218.25	12	−11.75
29	66 F	NPH 30	20	−10	212.75	212.25	9	−.5

weakness, itching and insomnia. The most common of these were nausea and nervousness. In the remaining 29 patients of this group no adverse symptoms were reported. The over-all incidence of significant side-effects in this group was therefore 14.7%. No attempt was made to reduce the dose (the usual therapeutic maneuver) and to try to continue these five patients in the study. In the other group, only one patient reported an episode of nausea and vomiting which was attributed to the tablets but which did not persist despite their continuation. The early impression concerning the identification of the tablets was confirmed at the conclusion of the study.

TABLE 4

Summary of Data—Placebo Group

	Age-Sex	Start Treatment	End Treatment	Insulin Change	Weight Start, lbs.	Weight End, lbs.	Weeks Treated	Weight Change, lbs.
1	51 F	NPH 35	50	−15	181.75	173.75	10	−8
2	61 M	NPH 75	70	−5	206.75	206	16	−.75
3	55 F	NPH 15	15		185.75	188.5	14	+2.75
4	77 F	Diet	Diet		212.5	209	10	−3.5
5	57 F	Tolbutamide			186.75	191.75	12	+5
6	50 F	Chlor-propamide			188.5	187	9	−1.5
7	40 F	NPH 55	55		190.75	192	9	+1.25
8	56 F	Diet	Diet		189.75	185.5	8	−4.25
9	66 F	NPH 40	40		239.75	238.75	8	−1
10	36 F	NPH 65	55	−10	177	177.75	13	+.75
11	51 M	NPH 95	95		241.75	245.25	16	+3.5
12	45 F	NPH 130	130		215	223	17	+8
13	59 F	Diet	Diet		235.75	234	9	−1.75
14	51 F	NPH 15	10	−5	226	229	10	+3
15	42 F	NPH 40	35	−5	202	207.5	8	+5.5
16	48 F	Diet	Diet		172.5	168.25	9	−4.25
17	51 F	Tolbutamide			183.75	182.5	14	−1.25
18	42 F	NPH 20	15	−5	260	251.5	11	−8.5
19	60 F	NPH 25	20	−5	190	187.75	9	−2.25
20	48 F	Diet	Diet		173.75	175.25	11	+1.5
21	45 F	NPH 20	20		209.75	210	10	+.25
22	58 F	NPH 15	30	+15	184	181	11	−3
23	49 F	NPH 35	65	+30	177	174.25	9	−2.75
24	48 F	NPH 15	15		296.5	298.75	9	+2.25
25	59 F	NPH 10	10		189.25	186	9	−3.25

The remaining 54 patients in the two groups, 29 on phenmetrazine and 25 on placebo medication, were statistically analyzed as to age and type of diabetic control and found to be highly comparable (tables 1 and 2). The ages of all patients ranged from 34 to 77 years. Twenty patients (69%) of the phenmetrazine group were on insulin therapy. Their mean insulin dose at the beginning of the study was 42 units daily. In the 17 insulin patients (68%) of the placebo group, the mean dose was 42.3 units daily.

Twenty-seven of the 29 patients in the phenmetrazine group (93.1%) lost weight, ranging from 0.5 to 26.25 pounds. Two patients gained 7.25 and 2.75 pounds, respectively (table 3). If a weight loss of one-half pound

a week over a period of several weeks is accepted as significant, and not likely to be due to commonly seen minor weight fluctuations, then 20 of the 29 (68.9%) met this requirement. One patient lost almost three pounds a week over a period of nine weeks, and losses of one pound a week or better were seen in 12 of the 29 patients. The mean weight loss per week per patient in this group was 0.78 pound (table 5).

TABLE 5

Comparison of Results

	Phenmetrazine	Placebo
Number of patients	32*	25
Mean length of therapy (weeks)	9.7	10.8
Mean weight loss per patient (lbs.)	7.4	0.5
Mean weight loss per week per patient (lbs.)	0.78†	0.07†

* Includes three patients who were switched to phenmetrazine after a full course of placebo without effect.

† The weight loss on phenmetrazine was statistically significant at the 0.1% level, while the loss on placebo was not significant. The difference was also significant at the 0.1% level.

In the placebo group (table 4) 15 patients (60%) lost weight while 10 patients (40%) gained. However, only three of the 15 who lost weight (or 12% of the group) lost a half-pound a week or more. The other weight losses were small enough to be due to chance weight fluctuations. The mean weight loss per week per patient in this group was 0.07 pound (table 5).

Although these patients were not selected with regard to the mildness or severity of their diabetes, of the 20 patients taking insulin in the phen-

TABLE 6

Effect of Therapy on Insulin Dosage

	Phenmetrazine	Placebo
Total number of insulin patients	20	17
Able to discontinue insulin	5 (25%)	0
Insulin reduced 50 to 100%	10 (50%)	0
Mean insulin change (units)	−18.2*	+1.5†

* Includes two switched patients.

† The change in insulin dosage in the patients on phenmetrazine was statistically significant at the 0.1% level, while that in the placebo group was not significant. The difference was also significant at the 0.1% level.

metrazine group, five (25%) were able to discontinue insulin entirely during the period of observation: two taking 30 units daily, and one each taking 40 units, 20 units and 15 units daily. Five additional patients had their insulin requirements reduced by 50% or more. Thus a total of 50% of the whole group reduced their insulin dosage from 50 to 100%. None of the patients in the placebo group taking insulin had a significant reduction in insulin requirement. The mean insulin change in the phenmetrazine group was minus 18.2 units, while in the placebo group it increased 1.5 units daily (table 6).

Three of the patients in the placebo group were switched over to the apparently active medication entirely without their knowledge at the conclusion of an adequate period of observation. This was done even though at this point the code had not been furnished. In each case the results were statistically significant. Case 1, controlled on tolbutamide, after 14 weeks of placebo medication had lost 1.25 pounds. She was then placed on phenmetrazine, and in eight weeks lost 4.5 pounds, or 0.56 pound a week. Case 2, on NPH insulin, 15 units daily, had gained 2.25 pounds after nine weeks on placebo. She then lost 4.75 pounds after nine weeks on phenmetrazine, or 0.53 pound a week. Her insulin was reduced from 15 units daily to 10. Case 3 had lost 0.75 pound after 16 weeks on placebo. His insulin dosage had varied from 75 units of NPH daily to 70 units. At the conclusion of nine weeks on the anorexiant he had lost 10.5 pounds (1.17 pounds a week), and was well controlled on 30 units of insulin daily. This last result was even more remarkable in view of the fact that during eight years of attendance at the diabetic clinic this patient had never been able to reduce his weight despite our most strenuous efforts and his own earnest intentions. The addition of these three cases to the phenmetrazine group would bring the percentage of patients who lost weight significantly to 71.9.

Discussion

Some clinicians believe that anorexigenic drugs do not actually exert an appetite-suppressant effect, and that whatever effect they may have in producing a reduction in caloric intake, and thereby in weight reduction, is probably purely psychogenic.[17] It is readily agreed that the psychologic impact of prescribing a medication for a patient to "help him lose weight" or "control his appetite," and the extra time and attention given by the physician, are sometimes potent factors. The occasional success of the placebo-type compound sold in all drugstores, without prescription, and advertised blatantly with fantastic and entirely misleading claims, including the elimination of dietary restrictions, is ample evidence of the effect of such suggestion.

In the present study the effect of suggestion on caloric intake was carefully eliminated by scrupulous avoidance of any hint of a possible effect of the medication on appetite, and even the avoidance (for test purposes only) of the reactivation of old diet prescriptions or mention of the word "diet." The small incidence of placebo-reactors (12%) and almost complete absence of placebo side-effects may be indirect evidence of the success of this oblique deception. Obviously, under normal conditions, the major stress would have been placed on diet and the anorexiant properly categorized as a useful and possibly intermittent adjuvant. It is therefore a justifiable conclusion that the striking effectiveness of phenmetrazine was due to a pharmacologic action, presumably on the appetite centers of the subcortical area, with the production of varying degrees of anorexia.[18, 19, 20] This led to an involun-

tary reduction in caloric intake sufficient to overcome the multiple factors producing and maintaining a positive weight balance in more than 70% of the test group. It seems fair to assume that the appetite-suppressant action of phenmetrazine, when added to a properly prescribed dietary régime, would produce greater weight loss in an even larger percentage of cases than it did unaided as an unknown. Increases in dosage where indicated and tolerated, and decreases where not so well tolerated, might also increase the number of successes and decrease the number of failures.

The value and effectiveness of incorporating, with minimal risk far outweighed by potential benefits, a pharmacologically active anorexigenic agent in the routine management of obese diabetics appear to have been established by the results obtained. However, total evaluation of any therapeutic agent or modality in the treatment of obesity and diabetes mellitus, *both* of which are diseases requiring lifetime control, must be made over a period of years, not weeks or months. The relapse rate, effectiveness of reinstituted courses and possible development of tolerance should be made matters of careful, long-term observation. Stimulation in the direction of such observations has certainly been furnished by the gratifying short-term results. In our present state of ignorance regarding the physiologic mechanisms of action of oral hypoglycemic agents, as well as their long-term effects on the course of diabetes mellitus, it would seem that the treatment of diet plus anorexigenic medication whenever applicable holds promise of greater ultimate benefit to the obese diabetic.

Summary

1. The importance of weight reduction to control maturity-onset, mild, obese diabetics needs reëmphasis because of the widespread use and abuse of oral hypoglycemic agents.

2. Proof of the frequent amelioration or total reversal of the diabetic state and of improvement in the over-all health status by correction of concomitant obesity is irrefutable.

3. In the treatment of obesity-diabetes, a practical and effective substitute, for both patient-incentive and psychiatric treatment, directed toward the obesity, is indicated more than is a substitute for insulin therapy. The latter corrects only the hyperglycemia and may, by itself, actually encourage obesity. Recent reports on the safety and anorexiant activity of phenmetrazine hydrochloride suggested that drug for a controlled investigation in this type of diabetic patient.

4. A triple-blind study was performed, starting with 80 obese diabetic clinic patients. The third blind portion, added to the usual double-blind procedure, was total unawareness by the patients of any relationship of the medication to appetite or caloric intake. In this manner the effect of suggestion was reduced to a minimum, if not eliminated.

5. The incidence of significant side-effects in the phenmetrazine group was 14.7%. In those completing the trial, 71.9% lost a significant amount of weight, as opposed to 12% of the placebo group. Fifty per cent of the insulin-taking patients in the phenmetrazine group had their insulin dosage reduced 50 to 100%, as opposed to none of the placebo group.

6. The value of routine utilization of a pharmacologically active anorexigenic agent such as phenmetrazine hydrochloride in the management of obesity-diabetes appears to have been established by the results obtained. At this time it would seem to be preferable to oral hypoglycemic agents in such patients.

SUMMARIO IN INTERLINGUA

A causa del uso general e del periculo potential del abuso de oral agentes hypoglycemic, il es necessari signalar de novo e emphaticamente le importantia del reduction del peso in le controlo de leve diabete in subjectos obese in qui le morbo se ha declarate post le attingimento del maturitate. Il es facto ben establite ab longe tempore que diabete es frequentemente multo meliorate e mesmo completemente corrigite (ben que non curate), durante que le stato del sanitate general es similemente meliorate, si le concomitante obesitate es tractate a bon successo. In le reduction del peso de diabeticos obese, le uso de agentes anorexigene es un substituto practic pro restrictiones dietari le efficacia del quales depende del initiativa del patiente mesme. Le reduction del peso de tal patientes es plus importante que le reduction del sucro del sanguine per medio de un agente hypoglycemic oral o per medio de un therapia a insulina. Iste ultimes corrige solmente le hyperglycemia e de facto servi possibilemente a incoragiar le mantenentia del obesitate. Recente reportos de un innocente effecto anorexigene de hydrochloruro de phenmetrazina ha inspirate le selection de ille droga pro un studio controlate in le mentionate type de patiente diabetic.

Le usual methodo bis-occulte esseva usate, initialmente con 80 obese diabeticos de clinica. Un factor de occultation additional esseva le complete ignorantia del patientes con respecto al relation inter le medicamento e lor appetito o ingestion caloric. Assi le possibilitate de un effecto suggestive esseva reducite al minimo o mesmo eliminate completemente. Inter le casos in que le essayo esseva completate, 71,9% del recipientes de phenmetrazina perdeva un quantitate significative de peso, per contrasto con 12% in le gruppo recipiente un placebo. In 50% del patientes recipiente insulina in le gruppo a phenmetrazina, le dosage de insulina poteva esser reducite per inter 50 e 100%, per contrasto con zero pro cento in le gruppo a placebo. Le incidentia de significative effectos lateral in le gruppo a phenmetrazina esseva 14,7%.

Il pare que le resultatos obtenite in le presente investigation demonstra le valor del utilisation routinari de pharmacologicamente active agentes anorexigene del typo de hydrochloruro de phenmetrazina in le regime de obese diabeticos. Al presente tempore, isto pare preferibile al uso de oral agentes hypoglycemic in multe tal casos.

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SOME OBSERVATIONS ON THE USE OF CHLORPROPAMIDE IN PRIMARY TOLBUTAMIDE-FAILURE DIABETICS * †

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Chlorpropamide is a new oral sulfonylurea. Like tolbutamide, the other sulfonylurea presently available in the United States, chlorpropamide has no antibacterial activity. It is rapidly absorbed from the gastrointestinal tract of man; within one hour after a single oral dose it attains readily detectable blood levels,[1] which reach a peak within two to four hours.[2, 3]

Chlorpropamide blood levels diminish gradually, the drug being excreted slowly in the urine as the active hypoglycemic material. Within 96 hours, in man, 65 to 90% of a single oral dose of chlorpropamide is excreted in the urine.[1]

The half-time of its disappearance from the serum after a single 0.5 gm. dose has been found variously to be 35 or 36 hours, or about eight times that of tolbutamide.[4] The evidence indicates that chlorpropamide is bound to protein in the blood.[1]

Unlike tolbutamide, chlorpropamide is not deactivated in the human. The parachloro substituent contributes to the longer action of chlorpropamide by preventing its oxidation to an inactive metabolite. This characteristic, and its slow urinary excretion, have permitted once-a-day medication, with maintenance of relatively constant blood levels and therapeutic activity.

A group of 13 previously studied tolbutamide-failure diabetics was studied again. With the exception of four private patients (one a brittle diabetic who had never been on tolbutamide), all had been subjects in 1957 of a study of the effects of tolbutamide, carried out in conjunction with Dr. Stuart Blauner, in the clinic of the White Plains Hospital. At that time we were interested in determining whether an intravenous tolbutamide test was of value in screening patients for the use of tolbutamide. As a result of that study it was concluded that a satisfactory correlation between the intravenous tolbutamide test and the subsequent clinical course on oral tolbutamide was not sufficiently high to warrant the use of an intravenous tolbutamide test for screening patients. These patients (with the above exception) were all considered to be primary failures on the oral use of tolbutamide. It should be emphasized that the earlier study with tolbutamide was made on our

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This study of the effects of a new oral antidiabetic compound, chlorpropamide (Diabinese, Pfizer P-607) was carried out in the Metabolic Clinic of the White Plains Hospital, White Plains, N. Y., in 1958.

† This study was aided by a grant from Charles Pfizer & Co.

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cases with no change in their regimen except for the introduction of the new medication. In the present study the same procedure was followed, so that the cases are comparable.

In the present study we sought the answers to the following questions:

1. Will chlorpropamide be successful in treating cases where a previous sulfonylurea, tolbutamide, failed under similar clinical conditions?
2. Is there a positive correlation between the level of chlorpropamide in the blood and the patient's clinical response?
3. If there is such a correlation, will the blood level help in predicting the patient's clinical response?

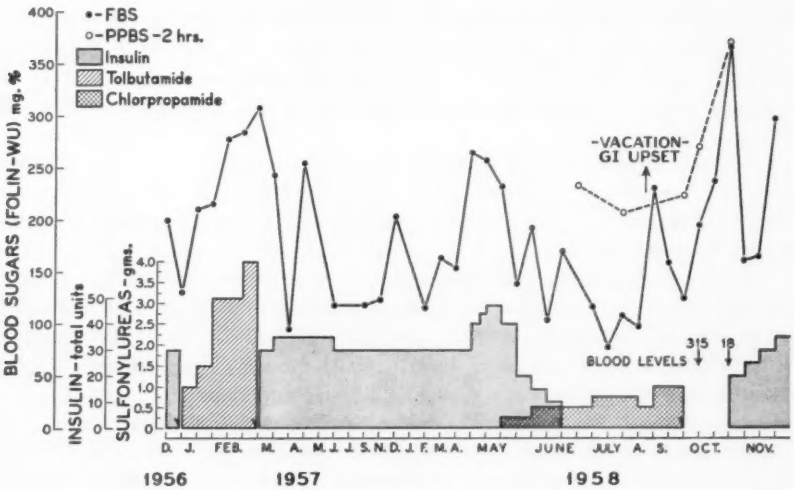


FIG. 1. Case 1.

CASE REPORTS

Case 1 (figure 1). A 56 year old married Negro female who had had diabetes for about 28 years had previously been stabilized on approximately 30 units of an insulin combination, with fasting blood sugars ranging from 150 to 200 mg.%. When she was put on tolbutamide in doses to a maximum of 4 gm. daily, fasting blood sugars climbed to over 300 mg.%, and it was concluded that she was a primary tolbutamide failure. As can be seen from figure 1, this experiment took approximately two months. Following this, the patient was returned to insulin. The fasting blood sugars then fluctuated rather widely (from 100 to 250 mg.%), requiring between 35 and 45 units of insulin. In May, 1958, administration of chlorpropamide was started and insulin reduced, so that by June the patient was receiving no insulin. The daily dose of chlorpropamide was 0.5 to 0.75 gm. On this routine, fasting blood sugars gradually fell to the range of approximately 100 mg.%. During her vacation in August she had a gastrointestinal upset and stopped taking her chlorpropamide, with a consequent rise in fasting blood sugar. This was promptly corrected once chlorpropamide was reinstituted (at the level of 1 gm. per day). By mid-September her

fasting blood sugar was approximately 125 mg.%. However, her serum glutamic pyruvate transaminase level (SGPT), which had been normal at the start of the experiment, had gradually risen until it reached 95 units; therefore, chlorpropamide was discontinued. One week later her chlorpropamide level was still 350 gamma%. At this time her fasting blood sugar had climbed to 200 mg.%. In the ensuing two weeks her chlorpropamide level fell to 18 gamma% and the SGPT returned to normal, but her fasting blood sugar rose to over 350 mg.%. Administration of insulin was therefore begun again. At the present time the patient is stabilized on an insulin mixture of approximately 38 units per day.

This patient also had an interesting side-effect. She developed a papular rash which was considered to be a result of the chlorpropamide. Biopsy was reported as consistent with dermatitis medicamentosa. However, a scratch test and an intradermal skin test for chlorpropamide sensitivity were negative.

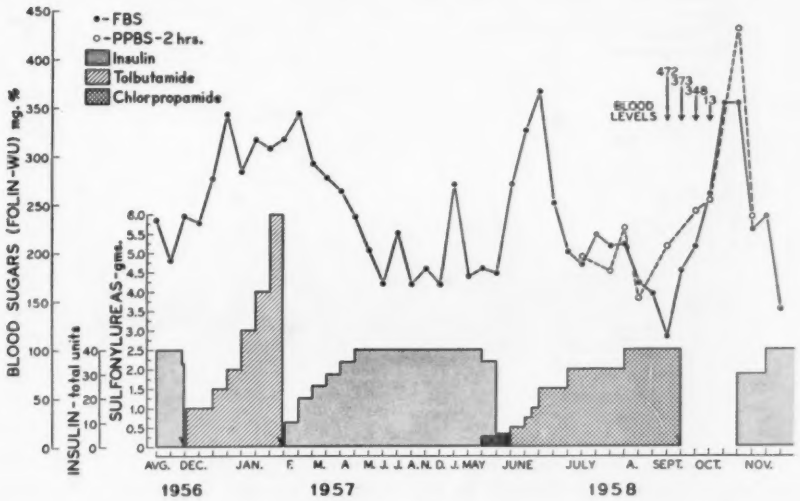


FIG. 2. Case 2.

Summary: This patient was a primary tolbutamide failure. On doses of chlorpropamide in the range of 0.5 to 1 gm. per day, better blood sugar control was achieved than had been previously achieved on 30 to 40 units of insulin per day. She had a probable dermatitis medicamentosa, which, however, has persisted to the date of writing (approximately three months after cessation of all medication). Another interesting finding was the presence of an elevation of the SGPT, which promptly returned to normal following cessation of chlorpropamide.

Case 2 (figure 2). A 46 year old married Negro female who had had diabetes for five years had been poorly controlled on approximately 40 units of insulin daily; her fasting blood sugars ranged from 200 to 250 mg.%. On tolbutamide, with cessation of insulin, fasting blood sugars gradually climbed to over 300 mg.%. This occurred despite tolbutamide given in doses of up to 6 gm. daily. Following the

reinstitution of insulin in doses of up to 40 units daily, fasting blood sugars once again ranged from 175 to 200 to 250 mg.%. The patient was started on chlorpropamide and, as can be seen from figure 2, her fasting blood sugars promptly climbed to over 350 mg.%, while chlorpropamide was gradually increased to 2.0 gm. daily. On this, her blood sugars ranged around 200 mg.%. When chlorpropamide was increased to 2.5 gm. per day, fasting blood sugars fell to the range of 100 to 150 mg.%. These effects were achieved with chlorpropamide blood levels of between 348 and 472 gamma%. On the cessation of chlorpropamide therapy, fasting blood sugars promptly rose to a peak of approximately 250 mg.%, with a two-hour postprandial blood sugar of over 400 mg.%. When insulin was reinstituted, her fasting blood sugar and postprandial blood sugar promptly fell (figure 2).

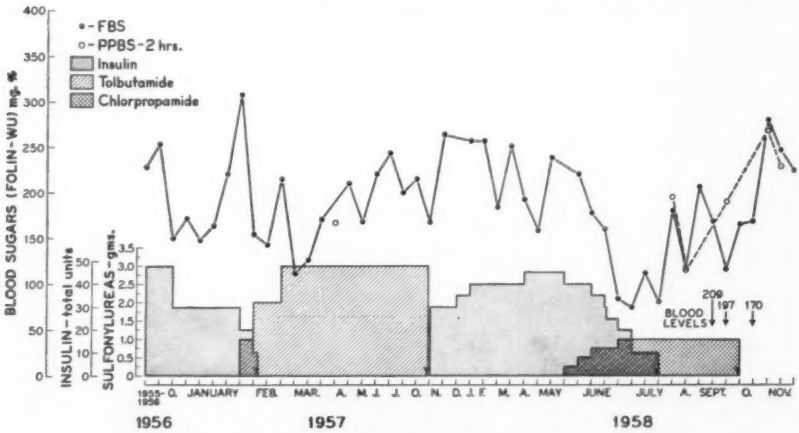


FIG. 3. Case 3.

Summary: This patient required extremely high dosages (2.5 gm. per day) to achieve a satisfactory effect. On this dosage, however, she had a better clinical status than previously, on a combined insulin dosage of 40 units per day. This high dose of chlorpropamide is not recommended for routine use. This was a special experimental situation to evaluate the effects of this high dose.

Case 3 (*figure 3*). A 50 year old married Negro female, a known epileptic on Dilantin and Phenobarbital, had had diabetes for 16 years. She had previously been moderately well controlled with approximately 30 units of insulin per day, on which fasting blood sugars ranged around 150 mg.%. On tolbutamide, in dosages of up to 3 gm. per day, her fasting blood sugars gradually climbed so that they ranged between 150 and 240 mg.%, and it was felt that she was a tolbutamide failure. When insulin was reintroduced, in dosages of up to 45 units per day, her blood sugars gradually fell somewhat, but were still felt to be not entirely satisfactory, ranging between 150 and 225 mg.%. On the institution of chlorpropamide in conjunction with the insulin, a rather marked fall of blood sugar was obtained, and fasting blood sugars in the range of 100 mg.% were easily obtained. When insulin was totally discontinued, however, her blood sugars gradually climbed to the range of 125 to 200 mg.%, but

were not so high as her blood sugar levels on either tolbutamide alone or insulin alone. Following the cessation of chlorpropamide therapy the fasting blood sugar promptly climbed to over 250 mg.%.

Summary: This patient represents one with poor control, both on tolbutamide and on insulin; she achieved her best control on a combination of chlorpropamide and insulin, but even on chlorpropamide alone she achieved better results than on insulin (up to 40 units per day), or on tolbutamide alone.

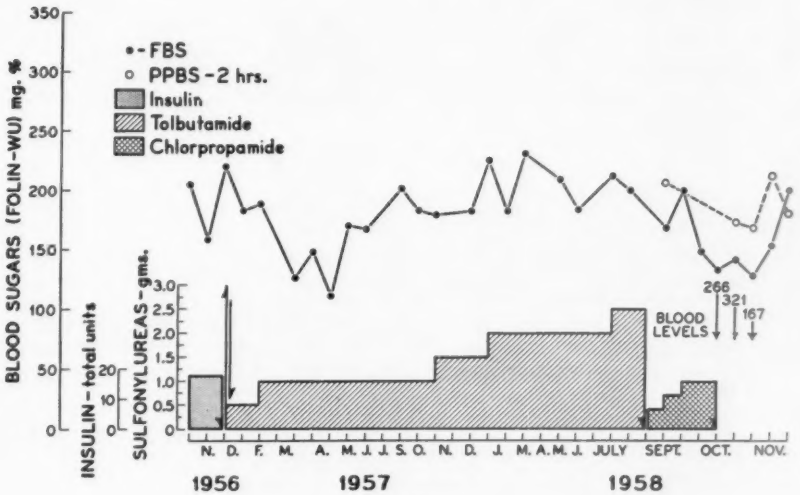


FIG. 4. Case 4.

Case 4 (*figure 4*). A 55 year old married Negro male who had had diabetes for approximately three years was rather poorly controlled on approximately 20 units of insulin per day, with fasting sugars ranging from 150 to 225 mg.%. With tolbutamide dosage, gradually increased to 2 gm. per day, his blood sugars remained in much the same range. Following the institution of chlorpropamide therapy, in dosages of up to 1 gm. per day, his fasting blood sugars gradually fell to a range of 125 to 150 mg.%. With the cessation of the administration of chlorpropamide, his fasting blood sugar promptly rose to previous levels. This patient also illustrates the fact that a significant chlorpropamide blood level may be continued by the patient for as long as two weeks after the cessation of therapy. On the date of cessation of therapy his chlorpropamide blood level was 266 gamma%; two weeks later his chlorpropamide blood level was still 167 gamma%. It is interesting to note that at this time his fasting blood sugar was still quite as good as it was one week earlier, with chlorpropamide blood levels twice as high (321 gamma%). With the ensuing fall in chlorpropamide level the blood sugar subsequently rose.

Summary: This patient illustrates a good response to chlorpropamide in moderately high dosage.

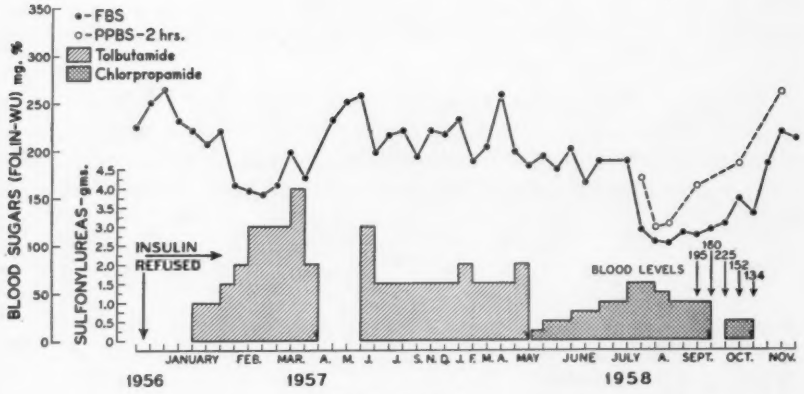


FIG. 5. Case 5.

Case 5 (*figure 5*). A 66 year old white married female who had had diabetes for 10 years had persistently refused to take insulin, and was only poorly controlled on diet, with fasting blood sugars ranging from 200 to 250 mg.%. On the institution of tolbutamide therapy there was some temporary fall in fasting blood sugars (to the range of 150 to 200 mg.%) but, as can be seen from figure 5, continued dosage of tolbutamide, in the range of 1.5 gm. per day, resulted in blood sugars averaging approximately 200 mg.%. Following the institution of chlorpropamide therapy in ascending dosages (to a maximum of 1.5 gm. per day), the fasting blood sugars fell,

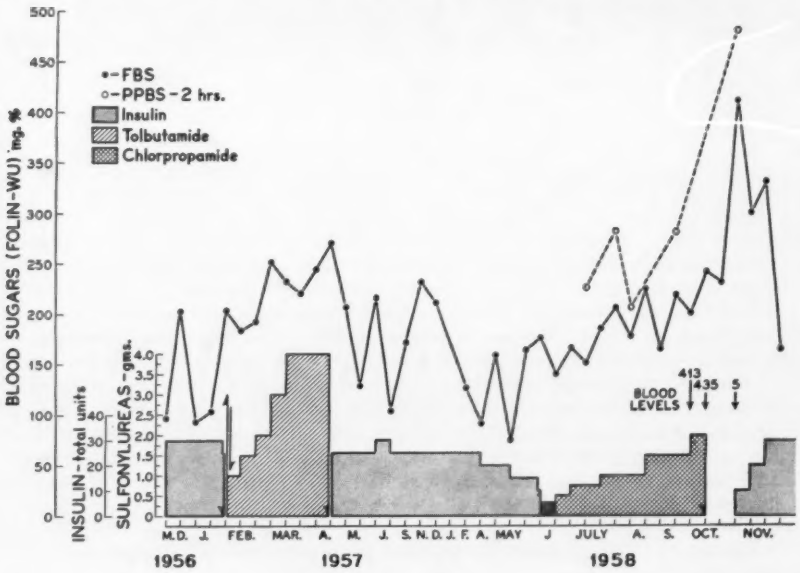


FIG. 6. Case 6.

and were maintained in the range of 100 mg.%. This good result was obtained despite the fact that the chlorpropamide blood level was never more than 225 gamma%. Following the cessation of chlorpropamide therapy the fasting blood sugars promptly rose again to pretreatment levels.

Summary: This represents an excellent result on a moderately high dose in a patient who had had a poor result on diet alone, as well as on diet plus tolbutamide.

Case 6 (*figure 6*). A 64 year old married Negro female who had had diabetes for approximately 26 years had previously been only moderately well controlled on a total insulin dosage of 30 units daily, fasting blood sugars ranging from 100 to 200 mg.%. On tolbutamide, in dosages of up to 4 gm. daily, her fasting blood sugars rose to 200 to 275 mg.%. Following the reinstitution of insulin therapy, at approximately the previous dosage, her fasting blood sugars gradually fell, fluctuating between 100 and 200 mg.%. With the introduction of chlorpropamide therapy, in gradually increasing dosage of up to 2 gm. per day, her fasting blood sugars gradually climbed, as can be seen in figure 6. At a peak chlorpropamide blood level of 435 gamma% her fasting blood sugar was approximately 250 mg.%. Following cessation of therapy, however, with a fall of chlorpropamide level to 5 gamma%, her fasting blood sugar rose to 400 mg.%, with a postprandial blood sugar of over 450 mg.%. With the reinstitution of insulin therapy her fasting blood sugar was promptly brought down to the range which had been maintained when the patient was on insulin.

Summary: This patient represents a chlorpropamide failure (despite some hypoglycemic effect), as well as a tolbutamide failure. Chlorpropamide failure occurred in face of extremely high blood levels, with a maximum of 435 gamma%.

Case 7. A 68 year old married white Puerto Rican female who had had diabetes for approximately five years had previously been inadequately controlled on tolbutamide, though it was recognized that she was extremely uncoöperative with regard to diet. Her fasting blood sugars ranged from 200 to 275 mg.%. On the institution of chlorpropamide, in gradually increasing dosages of up to 1.5 gm. per day, her fasting blood sugars varied between 135 and 210 mg.%.

Summary: This wholly uncoöperative patient was considered to be a failure on tolbutamide and also a relative failure on chlorpropamide, though the clinical control on chlorpropamide was superior to that on tolbutamide.

Case 8. A 71 year old married white female who had had diabetes for approximately 16 years had previously taken an average of about 38 units per day, with rather poor control, her fasting blood sugars averaging approximately 215 mg.%. Following the institution of tolbutamide therapy, in doses of up to 3 gm. per day, her fasting blood sugars averaged over 300 mg.%, and she was considered to be a tolbutamide failure. With the reinstitution of insulin, in dosages of 35 units per day, her fasting blood sugars were rather variable but ranged between 110 and 210 mg.%. The use of chlorpropamide, in dosages of up to 1 gm. per day, effected a partial reduction of her insulin requirements (from 35 to 20 units), her fasting blood sugars ranging from 125 to 175 mg.%. However, this patient refused to continue taking the medication, preferring to return to insulin.

Summary: This patient represents a tolbutamide failure who, on chlorpropamide, appeared to be making some improvement but who refused to continue taking the medication while we were reducing her insulin. It does not appear that she would have been successful in omitting insulin therapy, although she represents successfully combined insulin and chlorpropamide therapy.

Case 9. A 48 year old married white female who had had diabetes for approximately two years had previously been moderately well controlled on tolbutamide, 3.0 gm. daily, with fasting blood sugars of approximately 165 mg.%. On the institution of chlorpropamide therapy, at a dosage of 0.2 gm. daily, she had a fall in her fasting blood sugars to approximately 150 mg.%. It is interesting to note in this patient that in each of three tests her postprandial blood sugar was lower than the fasting: 154–94 mg.%, 153–116 mg.%, 181–149 mg.%.

Summary: This patient achieved excellent results on chlorpropamide in dosages of 0.2 gm. per day, as compared with a previous dosage of 3.0 gm. of tolbutamide.

Case 10. A highly intelligent 60 year old white married female, a winner of the Joslin Victory Medal, had had diabetes for approximately 27 years. She was an extremely brittle diabetic, requiring between 20 and 26 units of insulin daily in conjunction with a carefully controlled diet. Under the care of another physician she had been tried on tolbutamide and had been a complete failure, with a prompt development of glycosuria and ketosis such that she was returned to insulin. It was felt that a trial of chlorpropamide was desirable to determine whether her brittle status could be improved. However, despite increasing doses (up to 1.5 gm. daily), she was never able to lower her total insulin dosage below 18 units. On this routine she lost weight, had persistent glycosuria though no acetonuria, and did not feel well. On the reinstitution of insulin therapy she regained her lost weight and promptly felt as well as she had ever felt in the past.

Summary: In this patient, a winner of the Joslin Victory Medal, tolbutamide had previously been a failure. Chlorpropamide did not succeed in changing her brittle diabetic status, nor did it help in her control.

Case 11. A 25 year old white married female had had diabetes since age six. Under the care of another physician she had had trials with both tolbutamide and DBI ($N_1\beta$-phenethylbiguanide hydrochloride). On both of these she had been a failure, and had had to return to approximately 60 to 65 units of insulin daily. On this she regained her moderately good control. It is noted that she, too, was an extremely brittle diabetic. On chlorpropamide therapy, in doses of up to 2 gm. daily, it was not possible to reduce her insulin doses below 55 units per day. This patient also had prompt development of glycosuria, and did not feel well on the combined routine. The use of chlorpropamide did not succeed in ameliorating her brittle diabetic status.

Summary: This true juvenile diabetic, now an adult who had delivered a live, healthy baby approximately one and one-half years ago, had been a failure on tolbutamide and DBI. She was also a failure on chlorpropamide, which did not succeed in modifying her brittle diabetic status.

Case 12. A 58 year old white married female with known diabetes for 16 years was an extremely brittle, emotionally labile diabetic, requiring 30 units of total insulin dosage daily. She had not been tried on tolbutamide. The addition of chlorpropamide, in doses of up to 1.0 gm. per day, produced no improvement in her clinical status; chlorpropamide was considered to be a failure in this patient.

Case 13. A 25 year old white married female, the daughter of case 12, was discovered this year to be a diabetic. She had had a trial with diet, without adequate control of her diabetes. Following this, trial of tolbutamide, in doses of up to 2.0 gm. per day, achieved no better results. She was then given a trial of chlorpropamide, in dosages of up to 1.0 gm. per day, with no improvement. She was therefore considered to be a failure on both tolbutamide and chlorpropamide, and insulin therapy was started. On 30 units of insulin per day she achieved satisfactory control, with cessation of glycosuria and gradual regain of the weight she had lost at the onset of her diabetes and during the trial with the two sulfonylureas.

TABLE 1

Summary

Success	Failure (Partial*)	Failure
Case 1	Case 6	Case 8
Case 2	Case 7	Case 10
Case 3		Case 11
Case 4		Case 12
Case 5		Case 13
Case 9		

* Definite "hypoglycemic" response, though unsatisfactory clinical control.

Thus, of the group of 12 primary tolbutamide failures, six were successful on chlorpropamide. Of the six chlorpropamide failures in this selected group, two had some definite hypoglycemic response but were judged to be clinical failures. While the total number is small, a 50% success in an adversely selected group (tolbutamide failure) makes this new sulfonylurea very useful clinically (table 1).

DISCUSSION

This group of patients was selected in an attempt to determine the answers to three questions:

First, is it possible to achieve success with the use of chlorpropamide in the face of a previous tolbutamide failure? We may state that this certainly occurs, as evidenced by cases 1, 2, 4 and 5 (table 1). To this group might also be added case 3, who represents a greater success on combined chlorpropamide and insulin therapy than on chlorpropamide alone.

However, it is to be noted that cases 3, 6 and 7 represent failures of chlorpropamide alone. Case 6 is clearly a total failure, whereas case 3 may be said to be a relative failure, because her blood levels were certainly not significantly worse than they were when she was on approximately 40 units of insulin daily, while case 7 did better than on tolbutamide.

Second, is there a relationship between the success of the clinical response

and the blood level of chlorpropamide? It is clear from this study that, following the cessation of chlorpropamide therapy, lower blood levels of chlorpropamide were gradually obtained. At low levels, in several cases, the fasting blood sugars promptly escaped. It would appear that, in our successful studies, levels of between 134 and 225 or 266 gamma% were required for satisfactory blood sugar levels. These findings are in accord with those of many investigators,[5] and it is fair to state that there is probably a minimal effective blood level of chlorpropamide, which is most likely something over 100 gamma%. It is also noted in some of these cases that effective blood levels were maintained for from one to two weeks following the cessation of therapy, e.g., cases 4 and 3, and also case 5, for the one week in which she discontinued therapy, as noted on her chart. It may therefore be concluded, and has been well established, that chlorpropamide has a fairly substantial persistent blood level.

Third, if there is a relationship between the blood level and the blood sugar, is the blood level of significance in determining the clinical response? To this, the answer is no. It suffices to cite case 2, with blood levels of 348, 373 and 472 gamma%, with very satisfactory results, as opposed to case 6, with blood levels of 413 and 435, with unsatisfactory results. It is true that, in this latter case, the blood sugars rose on cessation of therapy; this, however, merely indicates that the patient had some antidiabetic effect from chlorpropamide, but it was obviously not satisfactory. It is perfectly clear that, while there is a minimal effective blood level, raising the blood level in some cases may be effective (case 2); but this is not consistently so, and high blood levels are no guarantee of a satisfactory clinical response.

The best method for the selection of patients who will probably be responsive still appears to be clinical trial. The patients likely to be responsive fall within the same general clinical categories as those previously described for tolbutamide and carbutamide. While it is true that some diabetics may be aided by combined therapy of chlorpropamide and insulin, as in our case 3, the brittle diabetics in our group were not significantly helped. Nonetheless, I feel that the use of sulfonylureas in brittle diabetics is worth a trial in each case. However, these patients require extremely careful and repeated clinical observation if they are not to go rapidly out of control. Duncan has suggested that those patients who show ketonuria within 24 hours following cessation of insulin will be failures.

Toxicity

All of the patients had the following laboratory procedures done prior to the institution of chlorpropamide therapy and at one or more times during the course of the experimental study: complete blood count, complete urinalysis, thymol turbidity and/or cephalin flocculation tests, alkaline phosphatase, total serum bilirubin, blood urea nitrogen and serum glutamic pyruvate transaminase (SGPT). These tests showed no significant change in any patient

in the course of the experiment, with the exception of case 1, who had a rise in the SGPT, which promptly fell to normal on cessation of therapy. This same patient was also the only one to manifest any skin toxicity; she developed a papular rash, the exact nature of which is not firmly established despite biopsy.

The metabolic effects of the sulfonylureas in experimental and clinical diabetes mellitus have been amply summarized in several extensive publications.[6, 7, 8]

Summary and Conclusions

1. Chlorpropamide appears to be a clinically effective hypoglycemic sulfonylurea in some diabetics. It was effective in six of 12 cases of previous primary failure on tolbutamide therapy.

2. Chlorpropamide appears to be effective in combination with insulin in some cases.

3. The oral dosage bears no firm, fixed relationship to the blood levels obtained. There appears to be a minimal effective blood level, probably between 100 and 200 gamma%, but raising the blood level beyond the minimal effective level does not always result in concomitant improvement of the patient's fasting blood sugar. While there is a rough correlation between the oral dosage and the blood level, the blood level is not more satisfactory than the patient's clinical response as measured by the blood sugar in determining the optimal dose. Until further knowledge of the long-term effects is obtained, it is certainly desirable to use minimal effective dosage.

4. In the three brittle diabetics studied, chlorpropamide was ineffective; it did not succeed in sufficiently reducing the amount of insulin needed or in ameliorating the patients' brittle status.

5. With one exception (case 1), no toxic effects were observed.

Summario in Interlingua

Chlorpropamida esseva administrate a 12 diabeticos qui non habeva respondite a cursos therapeutic con tolbutamida. Chlorpropamida esseva efficace in sex. Le droga etiam pare esser efficace in certe casos in combination con insulina. Le dosage oral non es firme- e fixemente relationate al resultante concentration in le sanguine. Il pare exister un minimo efficace de concentration del droga in le sanguine. Iste minimo se trova probabilemente inter 100 e 200 gamma pro 100 ml. Sed quando le concentration in le sanguine es augmentate in ultra del minimo efficace, le resultato non es in omne casos un concomitante melioration in le sucro sanguinee del patiente in stato jejun. Durante que il existe un grossier correlation inter le dosage oral e le concentration sanguinee, le concentration sanguinee non es plus precise que le responsa clinic del patiente (i.e. su sucro sanguinee) como guida in determinar le dosage optimal. Usque informationes additional con respecto al effectos a longe vista es obtenite in le uso de iste droga, il es certo desirabile restringer se al administration del minimo efficace. In le tres labile diabeticos includite in le studio, chlorpropamida esseva inefficace. Illo non succedeva a reducer sufficientemente le requiri-

mento de insulina o a stabilisar le stato del patiente. Effectos toxic esseva notate in solmente un del casos. In illo, signos suggerente damno hepatic e un eruption cutanee esseva notate.

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ON THE INCIDENCE OF SENILE OSTEOPOROSIS *

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Physicians generally agree that senile osteoporosis is encountered with increasing frequency, presumably due to the lengthening life span achieved during the last several decades. Back pain due to vertebral fracture is a common expression of this disorder, yet surprisingly little information is available regarding the incidence of vertebral atrophy in older persons. An opportunity to evaluate incidence was realized in our recent studies of adrenocortical function in patients with osteoporosis. Urinary 17-ketosteroid and 17-hydroxysteroid levels had been determined for a large number of women with symptomatic vertebral osteoporosis, but the data could not be interpreted for possible etiologic significance without similar observations for nonosteoporotic contemporaries. To obtain the latter, roentgenograms of the spines of 218 women were evaluated, and from this survey the present measure of incidence was derived. Although of limited scope, the survey was made of an ambulatory, nonhospitalized patient group, and the results are considered to be a better reflection of the incidence of osteoporosis in a general population than are the observations previously reported.[1, 2, 3] The distribution by age of osteoporotics found in the survey has been compared to that of a large group of osteoporotic women receiving treatment by the authors, and to the distribution in a similar series collected by Reifenstein [4] from the literature. The correlation of back symptoms with x-ray findings and the significance of early atrophy will be discussed.

Clinical Procedure and Material

The patients studied were 218 ambulatory women, over 45 years of age, attending the medical out-patient facilities of the Henry Ford Hospital. The majority were "new patients," seen for periodic health examinations or for nondisabling disorders. Excluded were patients with diseases which may result in osteoporosis, such as hyperthyroidism, rheumatoid arthritis, multiple myeloma, uncontrolled diabetes mellitus, or any illness requiring prolonged corticosteroid therapy. Also excluded from the tabulations were patients whose records indicated their selection for the x-ray survey despite clinical evidence suggesting the presence of osteoporosis. The roentgen

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TABLE 1

Roentgenographic Criteria Used in Rating Severity of Vertebral Osteoporosis

Indeterminate	Borderline or equivocal findings. Questionable loss of bone density and trabecular thinning. No vertebral body deformity.
Grade 1	Over-all density loss and trabecular thinning. End-plate accentuation and deformity. Early biconcavity and minimal vertebral wedging.
Grade 2	Further loss of density and of trabecular markings. End-plate deformities and biconcavities. Definite wedging of one or more vertebral bodies.
Grade 3	Severe demineralization. Extensive biconcavities. Marked wedging or collapse of several vertebral bodies.

evaluation of these patients was limited. A single lateral view of the dorsolumbar spine centered at the thoracolumbar junction was selected. The use of a step wedge was tried initially and an attempt made to assess the wedge itself, the wedge under the soft tissues and the wedge in contrast to bone density. This proved to be less rewarding than the direct inspection of the film itself without the wedge.

The classification of patients was relatively simple (table 1). Ratings were based on a definite demonstration of one or more of the following criteria: trabecular thinning, over-all loss of bone density, end-plate deformities and major vertebral body deformities. As the study progressed, however, the limitations of this method became apparent in determining which patients should be labeled normal and which should be labeled osteoporosis Grade I. Thirty patients were finally tabulated as indeterminate. The validity of this designation is supported by the fact that this group could be consistently separated from the normal and osteoporotic patients on repeated reëvaluation of films.

RESULTS

The incidence of osteoporosis has been tabulated for successive five-year age groups (table 2). Over-all, normal density of the dorsolumbar spine

TABLE 2

Incidence by X-ray of Vertebral Osteoporosis in 218 Ambulatory Female Patients

Age Groups	No. Pts.	Normal	Indeterminate	Grade			Per Cent
				1	2	3	
45–49	29	25	2	2	0	0	7
50–54	43	31	4	8	0	0	19
55–59	43	23	8	11	0	1	28
60–64	39	14	7	15	3	0	46
65–69	36	20	6	8	2	0	28
70–74	19	9	3	6	1	0	37
75–79	9	2	0	4	1	2	78
Totals	218	124	30	54	7	3	29
Per Cent		57	14				29

was found in 124 (57%), while 30 women had findings of indeterminate appearance. Sixty-four women (29%) had changes indicative of vertebral atrophy, yet only 10 of these (4.6% of the 218 total) had significant vertebral wedging or compression fractures. When incidence was determined according to successive five-year age groups, there was a progressive increase from 7% in the 45- to 49-year age group to 46% in women 60 to 64 years old, followed by a sharp drop to 28% for women age 65 to 69. The percentage increased again to a maximum of 78 for women over age 75. Two of the three patients with Grade III osteoporosis were in the last age group.

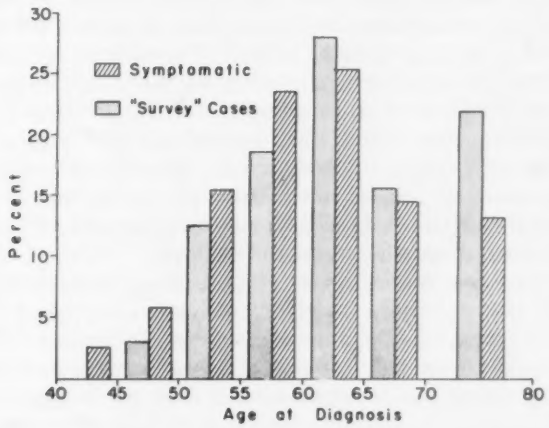


FIG. 1. Percentage distribution by age at the time of diagnosis of 64 women with osteoporosis diagnosed in the survey, and 123 women with symptomatic osteoporosis.

Figure 1 shows the percentage distribution by age at diagnosis of the 64 osteoporotics diagnosed in the x-ray survey, and of 123 women treated by the authors for symptomatic osteoporosis. Only 23% of the latter patients were under age 55, and the greatest number had been diagnosed between ages 60 and 65. As might be expected, a somewhat higher percentage of "survey" osteoporotics were in the older age groups, the greatest difference in distribution being noted for women age 70 to 80.

Back pain or distress of any kind was a major complaint for only three of the 124 women whose roentgenograms were indicative of normal vertebral density, although, when questioned, 24 women admitted having some form of back distress. Thus, a total of 27 nonosteoporotic women (22%) had symptoms possibly referable to the vertebral column. Nine of the 64 patients with x-ray-demonstrable osteoporosis listed back pain as the chief complaint, while 13 others acknowledged such distress when specifically questioned—a total of 22 women, or 34%. None of the three women with

Grade III osteoporosis mentioned back distress in her medical history. Of the 30 women in the indeterminate group, none had back pain as the chief complaint, while 10 acknowledged it as a frequently occurring symptom.

Comment

The validity of determining bone density by roentgenography as employed in the present study may be questioned. Although we recognize limitations in the method, no better means exist for studying large numbers of subjects. Biopsy is not practical for evaluating the bone status of asymptomatic patients on a large scale, although Gordan [5] has used this technic frequently in studying osteoporosis. The chief limitation of biopsy is that it samples only a limited area, and the skeleton is known not to manifest disease uniformly in a geographic sense. The step wedge as a density reference did not prove adequate to correct for the patient-to-patient variation in amount of soft tissue surrounding the vertebral column. Dent [6] has proposed a simultaneous x-ray of the subject and of a normal individual of the same sex, age, weight and body build. This technic, though theoretically reliable, cannot be utilized in extensive survey studies. Until a practical and accurate method is developed, bone density must be judged by the conventional roentgenographic method of the past.

Medical literature concerning osteoporosis has contained statements to the effect that 50% of women over age 50 have x-ray-apparent osteoporosis of the spine, and that one third have compression fractures.[3, 7] These are estimates projected from data of Gershon-Cohen [1] who determined by x-ray study the incidence of vertebral atrophy and fractures in aged persons confined to a rest home. Severe osteoporosis with resultant compression fractures of vertebral bodies was found by Gershon-Cohen and associates [1] in 29% of 82 women and 20% of 54 men whose ages ranged from 63 to 95 years. Similarly derived, an incidence of 45% was found by Vinther-Paulsen [2] in a survey of 33 residents in a Copenhagen home for the aged. Using the widely quoted data of Gershon-Cohen et al.,[1] Reifenstein [3] estimated that more than one-half of women over 50 years of age have x-ray evidence of decreased bone mass. The data of the present report do not appear to support these predictions, since only 29% of the 218 women were considered to have vertebral osteoporosis. However, in 14% or 30 subjects, the findings were indeterminate. If this rating is interpreted to mean early bone atrophy, an interpretation which could be defended in view of the known limitations of roentgenography in determining bone density, then 43% of women in the present study have bone atrophy. It is less biased to assume, however, that only one-half of the women in the indeterminate group actually had osteoporosis, albeit minimal. Adding these 15 to the 64 women with definite atrophy results in an over-all incidence of 36%, considerably less than the previous estimate of 50%.

That one woman in five, age 50 to 54, has vertebral atrophy is, perhaps,

the most significant finding of the present survey. One may reasonably question the clinical significance, present or potential, of the vertebral changes rated as Grade I osteoporosis. Are these indicative of an abnormal spine? We believe they are, and consider that an early x-ray diagnosis of osteoporosis often justifies the institution of endocrine and dietary therapy. When symptoms and x-rays indicate structural changes such as vertebral collapse, the osteoporosis is in its late stages. If there is justification for the use of anabolic hormone therapy in treating established osteoporosis, there are equal physiologic grounds for treating the women with early bone changes. There are reasons to believe that further progression of osteoporosis can be prevented with appropriate and sustained anabolic hormone therapy.[8, 9]

In a previous summary of 130 cases of women with vertebral osteoporosis collected from the literature, Reifenstein [4] noted that 23% were age 45 years or younger, and 63% were age 55 or less. As shown in figure 1, however, only 23% of 123 patients under treatment by the authors for symptomatic osteoporosis were under age 55, and the greatest number were diagnosed between 60 and 65. For the per cent distribution by age at diagnosis, the similarity between the symptomatic osteoporotics (cross-hatched columns) and the 64 survey osteoporotics (stippled columns) strengthens the validity of the survey findings. The distribution was similar in Cooke's [10] personal series of 43 osteoporotic women, 30% of whom were under age 60.

Only 15 women (7%) of the 218 in the present survey had vertebral wedging, and in five the changes were minimal. These are figures well below the previously mentioned 30% estimate for women over age 50, and more in keeping with the fact that, in round figures, only 50 women with senile and postmenopausal osteoporosis are indexed annually at the Henry Ford Hospital. If results are considered for only the women age 65 and over, to permit fair comparison with the findings of Gershon-Cohen and associates,[1] the incidence of vertebral fracture is still only 10%.

The significance of osteoporosis to back complaints is extremely difficult to evaluate. It has been estimated that symptoms relating to vertebral osteoporosis occur in 10% of women over age 50.[3] In the present survey, 5% of 218 women reported back pain as the chief complaint, while 22% mentioned back distress of some nature in the review of systems. Many women have back complaints without x-ray-apparent abnormality, and certainly there are others with asymptomatic yet significant vertebral atrophy, as evidenced by the fact that none of the women with Grade III osteoporosis had back distress. Physical activity of elderly women usually is limited, and acute strains intense enough to result in or aggravate vertebral fractures are for the most part not encountered. Indeed, the vertebral atrophy has probably been determined to some extent by the degree of inactivity. These considerations may explain the findings of Gershon-Cohen and associates [1] that many women in their survey were asymptomatic even with severe fractures. All were residents of an old age home, and it is likely that, in such

individuals, slowly progressive wedging of vertebrae occurs without inciting significant back distress.

Originally, Albright and associates [11] arbitrarily divided patients with osteoporosis into two groups, the postmenopausal and the senile, depending upon whether the onset was before or after age 65. Gonadal involution was considered to be the most significant etiologic factor for the postmenopausal type, and later a similar involution of the adrenal cortex for anabolic hormone production was postulated to be etiologically significant for senile osteoporosis.[12] These were distinctions of pathogenesis, not of histology or skeletal biochemistry, and postmenopausal osteoporosis is now generally

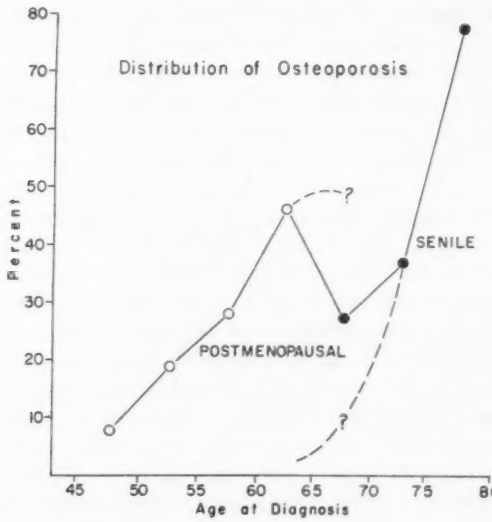


FIG. 2. Percentage incidence of osteoporosis by five-year age groups for 218 ambulatory female patients.

considered to be senile osteoporosis occurring earlier in life. Although Reifenstein [9] has mustered abundant data to support the Albright thesis that relative hypercorticism characterizes cases of senile osteoporosis, the etiologic significance of the data is inferential. It remains to be shown that gonadal involution is more important to the development of postmenopausal osteoporosis than is the loss of adrenal anabolic hormones, and that the latter contributes more to the development of senile osteoporosis than does gonadal arrest. Possible support for such a distinction of pathogenesis might be recognized, however, in the survey findings when the results are plotted graphically as per cent incidence according to five-year age groups (figure 2). A biphasic incidence curve is suggested. The first phase of the curve can be interpreted to represent osteoporosis resulting from gonadal

involution, with a peak incidence at 60 to 64 years, approximately 10 to 14 years after average physiologic menopause. According to rough calculations, this is the time required for osteoporosis to become apparent in x-rays when total skeletal calcium and average rates of calcium loss are considered.[4, 13] From these data it appears that women not biologically destined for postmenopausal osteoporosis do not develop bone atrophy until later years, when the more universal senile osteoporosis occurs following the decline of adrenal anabolic hormone secretion. This group is represented by the second phase of the incidence curve. Justification for this interpretation will require x-ray study of a much larger patient population, with parallel evaluation of both gonadal and adrenal function.

The present survey has not determined how frequently senile osteoporosis occurs in the general population, since the sampling was limited and many of the women were under medical supervision for one reason or another. It is probable that bone atrophy occurs more frequently in such a group than in the general population, even though patients were excluded whose illnesses are known to result in osteoporosis. The lessened physical activity necessitated by a variety of medical disorders possibly contributes to the development of bone atrophy. Expressed otherwise, vigorous and healthy women probably are less apt to seek even a routine physical examination than are women of less robust health, particularly those who may previously have required medical treatment. Our findings may not reflect the incidence of osteoporosis even in a general patient population, since many patients with back symptoms from vertebral atrophy or other cause consult orthopedic specialists directly. The removal of such women from the present survey of patients attending general medical clinics lowers the apparent incidence of osteoporosis. However, an average of only 50 women out of 40,000 new patients registered are indexed annually in our hospital records as having vertebral osteoporosis, senile or postmenopausal, and it is unlikely that the incidence found in the present study has been materially altered by the shunting away of these symptomatic osteoporotic women. The small decrease in incidence resulting from this loss of symptomatic patients from the survey probably does not offset the higher incidence found by survey of a patient rather than a community population.

A final qualifying comment relates to the possibility that ethnic or racial factors may be important in a consideration of incidence of osteoporosis. In treating women with symptomatic, senile osteoporosis, the authors have noted that the great majority have been of Anglo-Saxon origin, that only a rare patient has been "Latin," and that none has been Negro. The patient source is a heterogeneous population. Thus, of 155 women with known osteoporosis, Anglo-Saxon forebears constituted 71% of all forebears. Of 114 contemporary women without x-ray-apparent osteoporosis, the incidence of such ancestry was 53%. These observations have not been submitted to statistical study for significance. However, they do suggest that the

incidence of senile osteoporosis may vary from area to area, depending upon the racial or ethnic composition of the population under study.

In view of these several aspects, the results of the present survey are considered to be an approximation only of the incidence of osteoporosis for an ambulatory patient population of one institution.

Summary

X-ray-apparent osteoporosis of the spine has been found in 29% of ambulatory women age 45 and over. Only 4.6% had vertebral wedging or fracture. These incidences, though well below figures previously found by others in less representative surveys, emphasize the fact that osteoporosis is a major disorder in our aging population. Similar studies of much larger patient and general population groups may yield information of pathogenetic significance, particularly when data of clinical and biochemical nature are compared between osteoporotic and nonosteoporotic contemporaries. Accumulating evidence that anabolic hormone therapy may arrest symptomatic osteoporosis makes clinically significant the observation of early vertebral atrophy in otherwise normal, asymptomatic women.

Summario in Interlingua

Ben que plus sensibile methodos existe sin dubita, le studio roentgenographic remane le methodo le plus practic pro demonstrar osteoporosis in extense populationes de patientes. Tamen, pauc information existe relative al incidentia de atrophia vertebral in personas de etates plus avantiate. In consideration de iste facto, roentgenogrammas routinari del spina dorsolumbar de 218 ambulante femininas de etates de 45 annos o plus esseva evalutate con respecto a indicios de osteoporosis. Esseva concludite que le constatationes esseva normal in 124 casos (57%), indeterminate in 14%, e indicative de varie grados de osteoporosis in 64 casos (29%). Solmente 10 del feminas exhibiva cuneation vertebral o fracturas per compression. Le incidentia de osteoporosis cresceva initialmente ab un gruppo quinquenne de etate al proxime e attingeva un culmine de 46% in le gruppo de etates ab 60 a 64 annos. Illo redescendeva in le proxime duo gruppos quinquenne ante que illo attingeva su maximo de 78% in feminas de etates de 75 a 79 annos. Vinti-septe pro cento del feminas con normal densitate vertebral e 34% del osteoporoticas habeva symptomas dorsal, durante que le tres feminas con le plus avantiate alterationes structural esseva asymptomatic.

Le restringite numero de feminas in le studio, specialmente in le gruppos de etates plus avantiate, non justifica le formulation de conclusiones general. Tamen, le distribution del 64 osteoporoticas secundo lor etates es intimemente correlationate con illo del 123 feminas tractate per le autores pro "cognoscite" osteoporosis symptomatic, e isto reinfortia le validitate del resultatos del presente investigation. Le character biphasic del curva de incidentia es de accordo con le division traditional de osteoporosis in le typo postmenopausal e le typo senil.

Le signification de grados minimal de osteoporosis in le columna vertebral de subjectos asymptomatic non es cognoscite. Tamen, le crescente corpore de indicios que therapia hormonal es benefic in osteoporosis symptomatic rende le observation de un precoce atrophia vertebral plus que academic.

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PERCUTANEOUS SPLENOPORTAL VENOGRAPHY, WITH ADDITIONAL COMMENTS ON TRANSHEPATIC VENOGRAPHY * †

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Percutaneous splenoportal venography is defined as the radiographic demonstration of the splenoportal-intrahepatic venous circulation and its tributaries by means of the rapid transcutaneous injection of a radiopaque medium into the splenic substance. The method was first reported in dogs in 1951 by Abeatici and Campi,[1] and was applied to humans shortly thereafter. Independently, Bahnson and his co-workers had performed the procedure on six patients between 1949 and 1952, but their observations were not published until 1953.[2] In 1954, Atkinson and Sherlock measured the intrasplenic pressure percutaneously and found it to be a reliable index of the portal venous pressure.[3] Since these reports, many new data concerning the anatomy, pathology and physiology of the portal system have accumulated through the use of splenoportal venography.[4–22]

In the past, splenic and portal venography was employed at the Cincinnati General Hospital immediately prior to or during laparotomy. Since November, 1956, when the present study was initiated, percutaneous splenoportal venography has been carried out days or weeks prior to surgical intervention, and also in some patients in whom operation was not contemplated.

Technic

All patients are hospitalized for the study. Preliminary investigations include the usual hematologic studies and a urinalysis, the Quick one-stage prothrombin time, bleeding, clotting and clot retraction times, blood urea nitrogen, liver function tests § and serum albumin and globulin determinations, roentgen examination of the chest and upper gastrointestinal tract and, in the majority of the patients, needle biopsy of the liver.

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§ Thymol turbidity, thymol flocculation, cephalin-cholesterol flocculation, zinc sulfate turbidity, total lipids, prompt and total bilirubin, serum alkaline phosphatase and bromsulphalein retention. In some patients serum glutamic oxalacetic and pyruvic transaminase determinations were also obtained.

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On the day of the procedure the patient is maintained in the fasting state, cleansing enemas are administered, and appropriate premedication is given. Two units of cross-matched whole blood are made available. The patient is tested for sensitivity by intravenous administration of 1 c.c. of the undiluted contrast medium to be used, usually 70% sodium acetrizoate.

A preliminary scout film is made to insure that the exposure factors are adequate and that the liver, spleen, lower esophagus and upper abdomen are included on the film. A single-plane Schönander serial filming device with 14 by 14-inch films has been used for most of the studies. The films are exposed in the frontal plane, with the patient supine,* at the rate of one a second for five seconds, then one every two seconds for six seconds, making a total of eight exposures. More recently a 15-second exposure has been added, and even later exposures are recommended.[23, 24] A 15-minute pyelographic film should also be obtained. Manual film changing with fewer exposures has also proved to be satisfactory. Radiographic factors used are 300 milliamperes, 0.1 second and 85 to 115 kilovolts, at a film-target distance of 40 inches.

We have employed an intercostal approach except in patients with very large spleens, in whom a subcostal approach is used. With the patient supine, the selected site of puncture is cleansed, draped and infiltrated with procaine. In children and in those adults unable to coöperate adequately, general anesthesia with controlled respiration is used. A 3- or 3½-inch, 18-gauge needle, specially designed with four distal lateral holes, is inserted through the left ninth or tenth intercostal space in the midaxillary line, with stylet in place. The needle is directed medially and somewhat dorsocranially from the puncture site for a distance of 2½ to 3 inches while the patient holds his breath in mid- or full inspiration. Better results have been achieved with the tip of the needle near the splenic hilum, well away from its point of entry in the spleen.[6, 8] Movement of the needle with respiration and a steady drip of blood through its lumen on removal of the stylet confirm its intrasplenic position. It is important that the needle move freely with respiration, since its fixation in a rib has been responsible for laceration of the spleen.[25] A 10-inch long piece of flexible plastic tubing (with Luer-Lok connections), filled with saline, is locked to the needle hub and connected by a three-way stopcock to a saline-filled syringe.

Quiet breathing is permitted while the intrasplenic pressure is recorded from a base line 10 cm. above the table-top, using a fluid manometer which is connected to the stopcock by nonrigid tubing. Saline from the syringe is used to irrigate the system. The level of the meniscus is allowed to stabilize, except for slight variations during respiration, from higher as well as lower levels in the manometer. Free flow is necessary before an interpretation is made. Pressures are now recorded, frequently from several depths within

* The prone position can be used and may result in better visualization of the vessels in the left lobe of the liver. We have also performed one study with the patient upright, in an attempt to visualize additional collateral tributaries.

the splenic pulp. During a satisfactory manometric study the measurements will not vary more than 2 to 3 cm. We consider a level of less than 20 cm. of saline to be normal.

The manometer is now removed and the saline syringe replaced by one containing the contrast medium. During respiratory arrest 25 to 35 c.c. of the contrast medium are injected in four to six seconds and the needle is withdrawn. The first film is exposed when half of the contrast material has left the syringe.

The patient is kept in bed for 24 hours following the procedure, and closely observed for evidence of bleeding for the next five days. The first meal following the examination consists of clear liquids, but the usual diet is resumed thereafter.

Indications and Contraindications

In the present series, splenoportography was performed for the most part in patients being considered for portal-systemic venous shunt surgery, in an effort to differentiate between intrahepatic and extrahepatic block, and thereby to help to determine the type of operation indicated. It was also performed in selected cases with prior surgical portacaval anastomosis to determine the patency of the shunt, and in patients suspected of having esophageal varices. It has also proved to be of value in the localization of upper abdominal masses, in the study of cases with splenomegaly of unknown nature, and in the recognition of hepatic tumors.[5, 7, 8, 11, 15, 17-22, 26, 27, 28] It has also been advocated for the elucidation of ascites of unknown origin, and has been utilized for the demonstration of natural portal-systemic shunts in cirrhotic patients with neuropsychiatric manifestations.[17, 18, 29]

Contraindications to the performance of percutaneous splenoportal venography include the following: (1) inability of the patient to tolerate splenectomy; (2) sensitivity to the drugs to be employed; (3) renal insufficiency; (4) local disease along the needle pathway, such as left pleurisy with effusion; (5) bleeding tendency; (6) hemoglobin of less than 10 gm.%, and (7) splenic sepsis or conditions which predispose to rupture of the spleen (e.g., infectious mononucleosis). A Quick one-stage prothrombin determination of at least 50% of normal, and normal bleeding, clotting and clot retraction times are required. An impalpable spleen or the presence of ascites or mild jaundice does not preclude the study. If operation is to be performed immediately following the procedure, some of the contraindications listed above may be disregarded.

Complications

As with other technics employing intravascular contrast media, flushing, a metallic taste, nausea, vomiting and discomfort at the injection site have been encountered. Urticaria has been described,[18, 23] but no *serious* allergic

reaction has thus far been observed. At times a brief elevation of temperature results. Occasionally, reflux of the contrast substance along the needle tract or its accumulation beneath the splenic capsule is observed. This may be associated with a variable degree of left upper abdominal, chest or shoulder pain. Injection into the stomach, colon, kidney, liver and peritoneal and pleural cavities has been reported, and may result in considerable pain of variable duration.[2, 5-8, 16-20, 22-25, 27, 30] This might be obviated by a small test injection under fluoroscopic control.[24] Pneumothorax [20] and sepsis [24] have been recorded. Splenic infarction and hematoma, as well as intraperitoneal blood, have been observed at laparotomy.[2, 6, 16, 17, 19-22, 25, 26, 30-34] Thrombosis in the portal system as a result of the procedure has not been reported. Bleeding from esophageal varices within 36 hours after splenoportography has been recorded in four patients, but may well have been coincidental.[18, 35]

The most feared complication is splenic laceration with intraperitoneal hemorrhage. This has occurred as late as 16 days after the procedure.[36] Instances of major intraperitoneal bleeding secondary to percutaneous splenoportal venography occasionally occur.[6, 14, 18, 20, 23-26, 34, 35, 36] In some of these cases, splenectomy has been necessary to stop the hemorrhage, the remainder responding to blood transfusions. In several cases an unrecognized bleeding disorder was responsible for the hemorrhage.[20, 37] In others, inexperience of the operator, faulty technic or poor patient coöperation was apparently a major factor.[23, 25, 30] In still others, the information was insufficient for evaluating the cause.

Three deaths have been attributed to the procedure. One occurred in a seriously ill infant one-half hour after the procedure. Autopsy was not performed.[38] The second patient, a 78 year old man with leukemia, died 24 hours after splenoportography. Autopsy revealed a splenic laceration with hemoperitoneum and gastrointestinal bleeding from esophageal varices and gastric ulcerations.[35] In the third patient, death occurred from *Bacillus welchii* bacteremia 48 hours after a needle biopsy of the spleen and an unsuccessful attempt at splenoportography. The patient had a primary endothelioma of the spleen.[24]

Material

Between November, 1956, and May, 1958, 50 percutaneous splenoportal venograms with intrasplenic pressure determinations were attempted in 41 patients, ranging in age from three to 77 years. In an additional patient the intrasplenic pressure was measured but contrast medium was not injected. General anesthesia was necessary only in the three year old child. Table 1 lists the diagnoses in these 42 cases.

Ascites was present in seven patients, but the amount of peritoneal fluid was minimal at the time of the procedure in all but two. In 15 patients the spleen was impalpable; in two others its tip could be felt at the costal margin.

In the remainder the splenic edge was readily palpable 1 or more centimeters below the costal margin. There were nine patients with serum bilirubin levels ranging between 2.2 and 4.3 mg.%. In one patient with bile duct carcinoma the serum bilirubin was 29.5 mg.%. In the remainder, clinical icterus was absent and the total bilirubin did not exceed 1.7 mg.%. Hematemesis had occurred in 20 cases.

More than one splenic puncture was necessary in eight cases, three punctures being performed in three and two in five cases. No untoward effects were observed following the multiple punctures. In nine other cases the splenoportogram was repeated after an interval of from two days to 16 weeks.

TABLE 1

Diagnosis in 42 Patients

Cirrhosis of liver		27
Splenomegaly without cirrhosis		8
Undefined myeloproliferative disorder	1	
Polycythemia vera	1	
Cavernomatous transformation of portal vein	1	
Undetermined	5	
Fatty liver		2
Intrahepatic bile duct carcinoma		1
Pancreatic carcinoma		1
Pancreatic cyst		1
Thrombosis, superior vena cava		1
Thrombosis, inferior vena cava		1

RESULTS

Eight of the 50 examinations proved to be unsuccessful but, in most of these, reëxamination at a later date resulted in a satisfactory study. The chief cause of failure was subcapsular or extrasplenic injection, which occurred in five instances. The contrast material was accidentally injected into an enlarged left lobe of the liver in one case, while in another it was fortuitously injected into a splenic cyst (figure 11A). Useful information was obtained in both instances despite failure to inject the spleen, and there were no untoward sequelae. In the remaining case the unsuccessful study was attributable to x-ray equipment failure. In five of the eight cases the procedure was performed by inexperienced individuals. In three instances, attempts to puncture a normal sized spleen contributed to the failure.

No instance of splenic rupture or significant hemorrhage was encountered in this series.* In a number of cases, hemoglobin determinations obtained at varying intervals after the procedure showed no alteration. In two patients a transient fall in systolic blood pressure of about 20 mm. was

* Two such accidents have occurred since completion of this study, one controlled with transfusions and the other necessitating splenectomy. The latter was performed by an inexperienced operator. In neither case was there a recognizable abnormality in the bleeding or clotting mechanisms.

recorded shortly following splenoportography, but the hemoglobin and hematocrit values remained unchanged, and there was no increase in pulse rate. That these changes were not a result of the medication administered could not be excluded. In 20 cases, laparotomy was performed up to several weeks after the contrast study. In only two cases was an intraperitoneal hematoma found—in amounts of about 20 and 75 c.c., respectively. In 12 of the 20 cases the spleen was submitted for pathologic study. In the majority of these specimens, small intrasplenic infarcts or organizing hematomas were present.

Abdominal pain of varying severity and duration followed the procedure in a number of patients, but only 15 received analgesics for relief. The pain seldom lasted as long as 36 hours. In 15 cases, temperature elevations to 99.2° F. developed, but seldom persisted for more than a day or two. Four patients had abdominal pain, higher fever and moderate distention for about one week after splenoportography. In two of these the symptoms may well have been caused by coexisting conditions which antedated splenoportography.

In two patients a friction rub was detected over the spleen four and 12 days, respectively, after the procedure. In one case a small transient left pleural effusion developed after an extrasplenic injection of contrast medium, some of which had entered the extrapleural space.

The Normal Splenoportal Venogram

In eight patients a normal venogram was obtained. Three had splenomegaly of undetermined origin, two had Laennec's cirrhosis and fatty infiltration, two had chronic active hepatitis and posthepatitic cirrhosis, and one had obstruction of the superior vena cava with esophageal varices and extensive superficial venous collaterals. The intrasplenic pressures were normal in six of the eight, including three of the four with cirrhosis. The two patients with elevated pressures included the remaining cirrhotic and one of the cases of splenomegaly of undetermined nature.

The normal examination (figure 1A) demonstrates contrast material within the splenic pulp, the splenic and portal veins, and the intrahepatic portal venous ramifications. Reflux along the needle track may occur and the contrast material may spread under the capsule or over the surface of the spleen. Since the direction of blood flow within the portal venous tributaries is toward the liver, the superior and inferior mesenteric, the short gastric and the coronary veins are normally not filled with contrast medium. Anything more than the slightest reflux into these vessels is considered to be abnormal. Nonopacified blood entering the splenic and portal veins from these vessels often produces a streaming or jet effect, seen as a short, ill defined defect in the contrast column. This normal finding is to be differentiated from thrombosis.[13, 14, 16, 22]

There occurs a regular branching and reduction in caliber of the portal



FIG. 1. Normal percutaneous splenoportal venogram. A. (*above*) Venous phase. Note the streaming effect in the portal vein at the site of entry of the superior mesenteric. Intrasplenic pressure, 12 cm. B. (*below*) Hepatogram phase. Contrast medium remains in the splenic pulp, but there has been subcapsular leakage.

radicles within the liver. The detailed roentgen anatomy of these vessels has been described.[39] The late films show a diffuse opacification of the liver parenchyma, the sinusoidal phase or hepatogram (figure 1B). Delayed films may show the hepatic veins.[9] On the hepatogram the right lobe of the liver appears to be more radiopaque than the left, probably because the contrast-laden blood, heavier than blood alone, tends to accumulate in the more posterior right lobe.[9] Maximal opacity occurs centrally in the right lobe, where the liver substance is thickest. Splenoportal circulation times have been reported by others.[6, 9, 16]

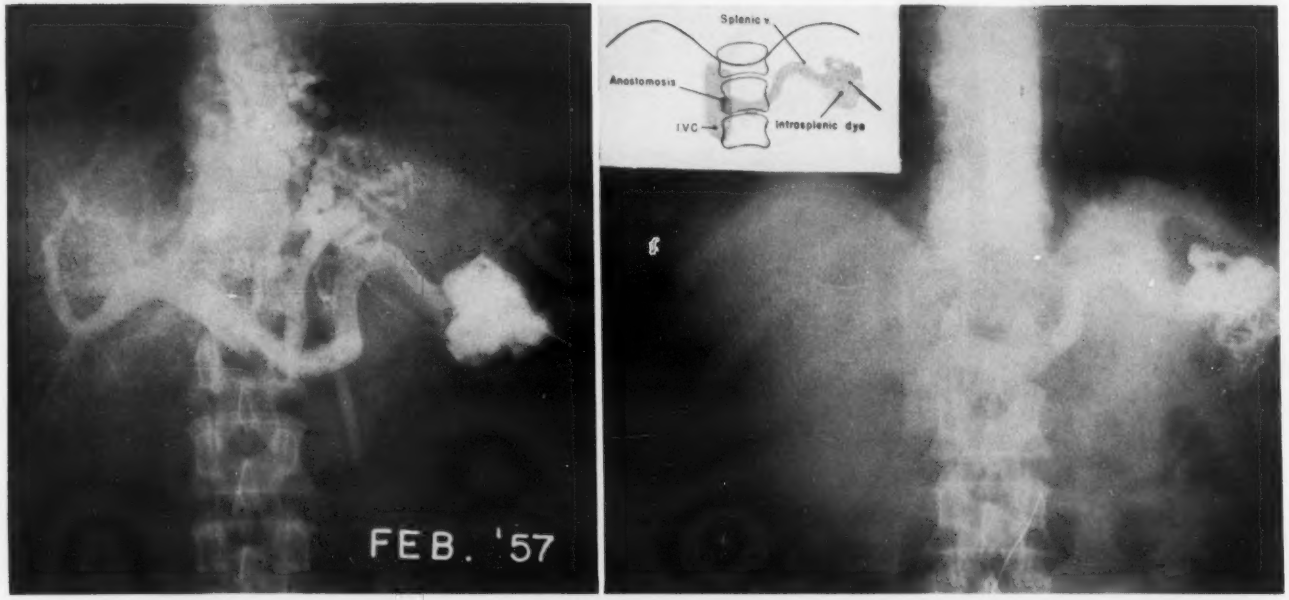
The Abnormal Splenoportal Venogram

Intrahepatic Portal Obstruction: The roentgen criteria for intrahepatic portal obstruction were (1) the demonstration of patent splenic and portal veins; (2) significant backflow into one of the mesenterics, the gastric coronary and/or other collateral veins; and (3) abnormalities of the intrahepatic venogram or the hepatogram, when present, consistent with the pattern of cirrhosis. It should be noted that suprahepatic venous obstruction, the result of constrictive pericarditis, hepatic vein thrombosis, etc., may present identical roentgen findings, but this was not encountered in the present series.[9, 21] The diameters of the portal and splenic veins have proved to be of little value in the recognition of intrahepatic obstruction. Roentgen evidence of intrahepatic portal obstruction was present in 20 patients: four with Laennec's cirrhosis, six with postnecrotic cirrhosis, three with posthepatitic cirrhosis, five with portal cirrhosis of unspecified type, one with fatty infiltration of the liver, and one with splenomegaly of undetermined etiology associated with carcinoma of the uterine cervix. The intrasplenic pressure was elevated (22.5 to 43.0 cm.) in all but three.

A variety of collateral veins was demonstrated in this group of patients (figures 2A, 11B). Perisplenic, short gastric, coronary, superior and inferior mesenteric and lumbar veins and their branches were commonly filled, often appearing to be dilated and tortuous. Gastric and esophageal varices were nearly always evident and usually quite large. Less often, diaphragmatic, intercostal, abdominal wall, umbilical, transhepatic and deep bridging vessels were also seen.

In cirrhosis, the intrahepatic portal ramifications may show attenuation, sparsity and irregularity. A mottled pattern may also be evident in the hepatogram.[9, 11, 15, 16, 20, 21, 22, 40]

Four patients were studied after end-to-side portacaval anastomosis. Two had Laennec's cirrhosis, one had postnecrotic cirrhosis, and the fourth had portal cirrhosis of an unspecified type. In one patient the esophageal varices and other collateral veins shown on the preoperative splenoportogram were no longer demonstrated postoperatively, and all of the contrast medium flowed via the shunt into the inferior vena cava (figure 2). The intrasplenic pressure fell from a preoperative level of 28.5 cm. to 16 cm. after operation.



A B

FIG. 2. Splenoportogram in Laennec's cirrhosis with bleeding varices. A. Preoperative study. The coronary and short gastric veins are dilated and there are gastric and esophageal varices. There is backflow into the inferior mesenteric vein. The portal radicles in the liver are attenuated. Intrasplenic pressure, 28.5 cm. B. Repeat study two months after portacaval shunt. The anastomosis is patent and there is no collateral filling. Splenic pressure, 16 cm.

Incidentally, the postoperative intrasplenic pressure was also measured with the patient in the upright position and found to be 30 cm. In this position the level of the needle was approximately 14 cm. below that of the right atrium.



FIG. 3. Splenoportogram in cirrhotic with recurrent bleeding three and one-half months after portacaval shunt. A. (*above*) Early film, showing marked constriction at site of anastomosis and backflow into coronary vein. B. (*below*) Late film. Bridging collaterals enter the liver. There are gastric and esophageal varices.

In another patient the splenic pressure, 35 cm. prior to the shunt, fell to 17 cm. postoperatively. Unfortunately, the splenoportogram was unsatisfactory.

In a third patient the portal pressure obtained during operation was 47 cm. Five weeks after the shunt the intrasplenic pressure was found to be only 8 cm. Contrast medium was not injected. The patient was operated upon again at a later date because of recurrent gastrointestinal bleeding and no evidence of bleeding from varices was found.

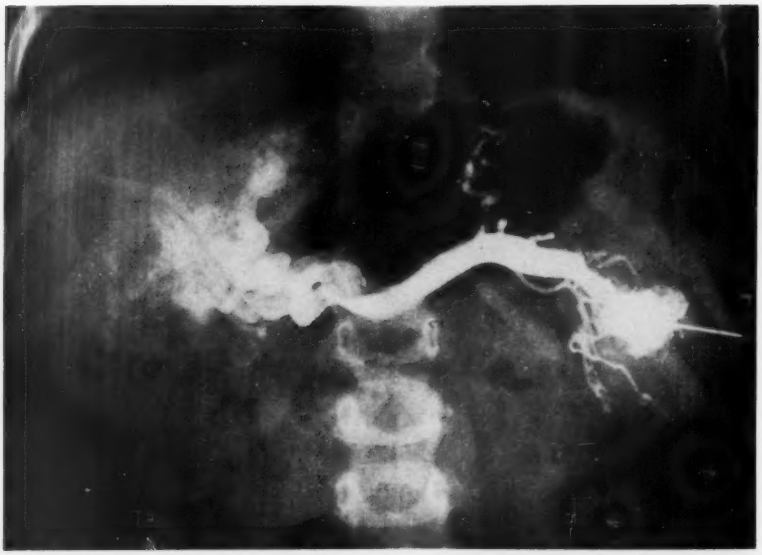


FIG. 4. Splenoportogram in three year old boy with normal liver function and bleeding varices. There are cavernomatous transformation of the portal vein and short gastric collaterals to the stomach.

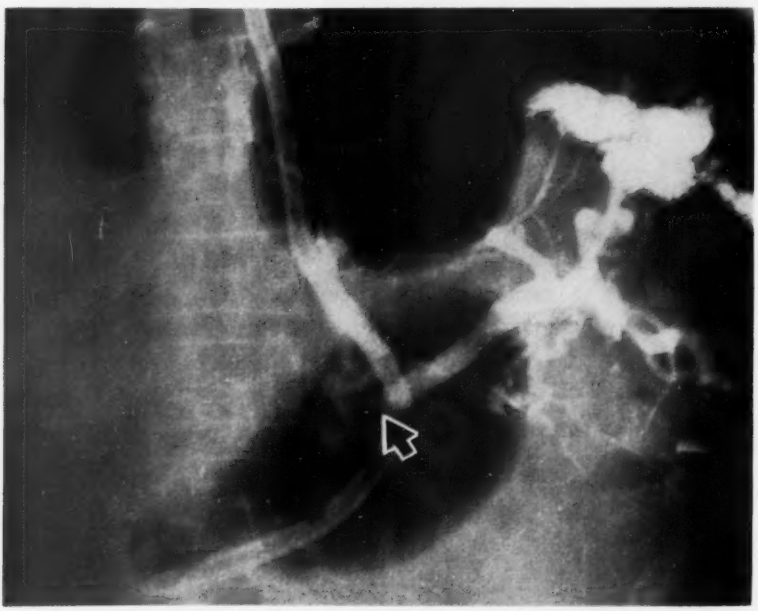


FIG. 5. Splenoportogram in Laennec's cirrhosis, with massive ascites and bleeding varices. Sengstaken-Blakemore tube with distended balloon in stomach. The column of contrast ends abruptly at the junction of the splenic and portal veins. There is a moderate degree of collateral filling. At autopsy the splenic and portal veins were patent.

In the fourth patient, at the time of portacaval anastomosis the omental vein pressure was 24 cm. Bleeding recurred three and one-half months later. Splenoportography demonstrated marked reduction in caliber of the stoma of the portacaval anastomosis, with collateral venous filling (figure 3). The splenic pressure was 24 cm. A splenorenal shunt was performed.



FIG. 6. A 52 year old male with myeloproliferative disorder and hepatosplenomegaly. The contrast medium fails to enter the splenic vein. Collateral filling via the capsule of the spleen. The intrasplenic pressure was 57 cm. A thrombus was found in the splenic vein at the hilum of the spleen at operation.

Extrahepatic Portal Obstruction: The demonstration of partial or complete block of the splenic or portal veins with filling of collateral venous channels is said to indicate extrahepatic obstruction of the portal system. The intrahepatic vessels, if seen, fill quite late through bridging collaterals or an obviously partially obstructed splenic or portal vein. As will be shown, however, failure of the contrast medium to enter the liver promptly via the portal vein is not always indicative of extrahepatic obstruction.

Eight patients demonstrated these criteria: In one, a three year old boy with hematemesis and normal liver function tests, cavernomatous trans-

formation of the portal vein was demonstrated (figure 4). In another case the entire portal vein failed to fill but no collaterals were demonstrated. Autopsy revealed extrinsic pressure on this vessel at the porta hepatis by a bile duct carcinoma, the vein being intrinsically patent. In a bleeding cirrhotic patient with massive ascites, and with an inflated intragastric balloon (without traction), the films revealed an abrupt termination of the contrast column in the proximal portal vein, but the vessel was found at autopsy to be normally patent (figure 5). In a patient with a myeloproliferative disorder, occlusion of the splenic vein was demonstrated by splenoportography

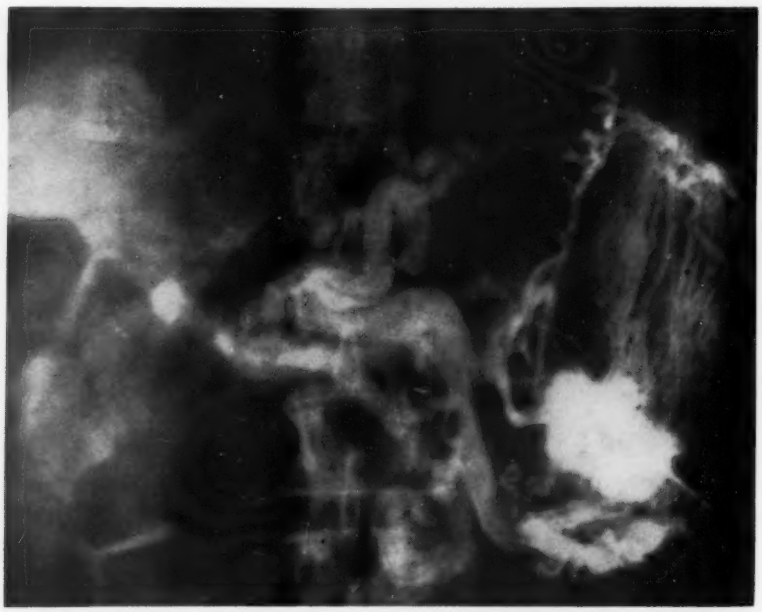


FIG. 7. Splenoportogram in 38 year old female with polycythemia vera, duodenal ulcer and hematemesis. Occlusion of the portal vein near the liver, with extensive collateral filling, including an arcade of perisplenic veins. Splenic pressure, 40 cm.

(figure 6). A thrombus was found at this site at operation. In the remaining four cases, operative proof as to cause was lacking. In two, contrast medium extended only as far as the proximal portion of the portal vein, in one the apparent block seemed to be in the splenic vein, and the fourth showed occlusion of the portal vein at the site of entry of the superior mesenteric (figure 7). In all four cases there was extensive collateral circulation.

In another patient with hepatic cirrhosis and bleeding esophageal varices (not one of the present series), a thrombus was outlined by contrast within the portal vein (figure 8). Surgical confirmation was obtained.

Splenic pressures were elevated in all but the patient with the bile duct carcinoma, in whom the pressure was only 18 cm. In the others the pressures varied from 24 to 65 cm.

Upper Abdominal Tumors: Because of the proximity of the pancreas to the splenic and portal veins, it is not surprising to find impingement upon these vessels by mass lesions of the pancreas. Figure 9 demonstrates torsion of the splenic vein by a large pancreatic cyst in a woman with recurrent hematemesis. The intrasplenic pressure was 24 cm. Since this series was completed, several additional cases were encountered where displacement of the portal vein by tumor was demonstrated. An example of compression of the portal vein by a bile duct carcinoma has already been described.

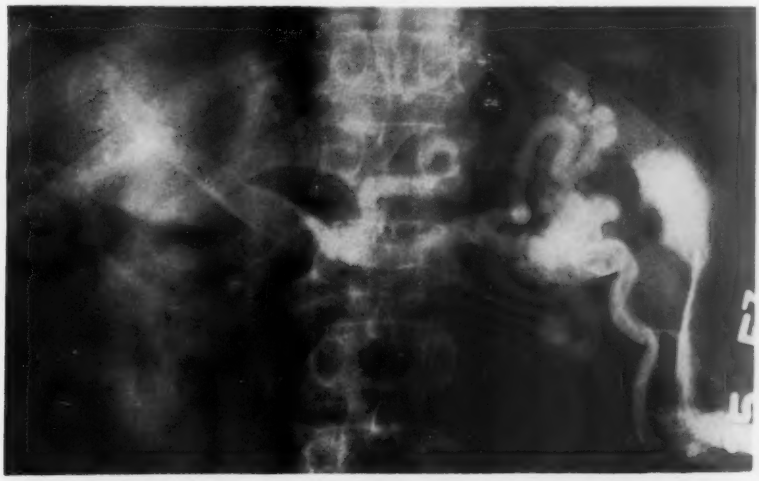


FIG. 8. Laennec's cirrhosis and bleeding varices. The radiolucent defect in the portal vein represents a thrombus, proved at operation. (Courtesy of Dr. Alfred Kierle, Cincinnati V. A. Hospital.)

Primary and metastatic neoplasms of the liver have been demonstrated by splenoportal venography. The malignant deposits are best seen on the later films as radiolucent filling defects within the diffusely opacified liver parenchyma. Displacement and occlusion of the larger portal radicles are less often shown. We have encountered such radiolucent defects in the hepatogram twice in the present series. In one case the defect was subsequently shown to be the site of a metastasis from a carcinoma of the distal pancreas (figure 10B). In the other case the defect corresponded to a mass which, at operation, proved to be a large regenerative nodule in a liver with postnecrotic cirrhosis (figure 11C). In another patient (not one of the series), multiple ill defined filling defects on the hepatogram strongly suggested the diagnosis of extensive liver metastases. However, a biopsy obtained at operation showed toxic hepatitis with lobules of fatty degeneration. In

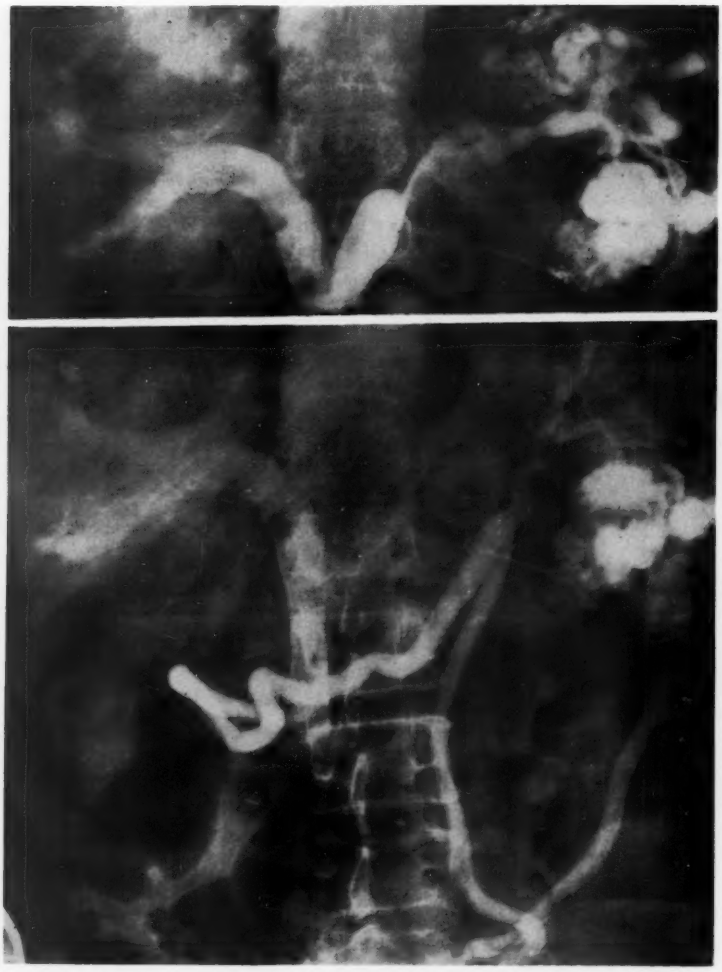


FIG. 9. Splenoportogram in 60 year old female with gastrointestinal bleeding. A. (*above*) Torsion of splenic vein by a large pancreatic cyst. There are extensive gastric varices. B. (*below*) Late film. A circuitous mesenteric vein gives off a gastric collateral and then enters the superior mesenteric vein to reopacify the portal vein.

another case a large area in the right lobe of the liver in a patient with known cirrhosis was thought to indicate a primary hepatoma. At operation a large mass of fibrous tissue of unknown etiology was found at the site of the defect.

PERCUTANEOUS TRANSHEPATIC VENOGRAPHY

In the patient in whom the contrast medium was accidentally injected into the left lobe of the liver, an excellent venogram was obtained, revealing

extrinsic compression of the left lobe by a mass in the region of the body and tail of the pancreas (figure 10A). An avascular area consistent with a metastatic nodule was seen within the right lobe of the liver (figure 10B). The diagnosis of carcinoma of the distal pancreas with hepatic metastasis was subsequently confirmed.

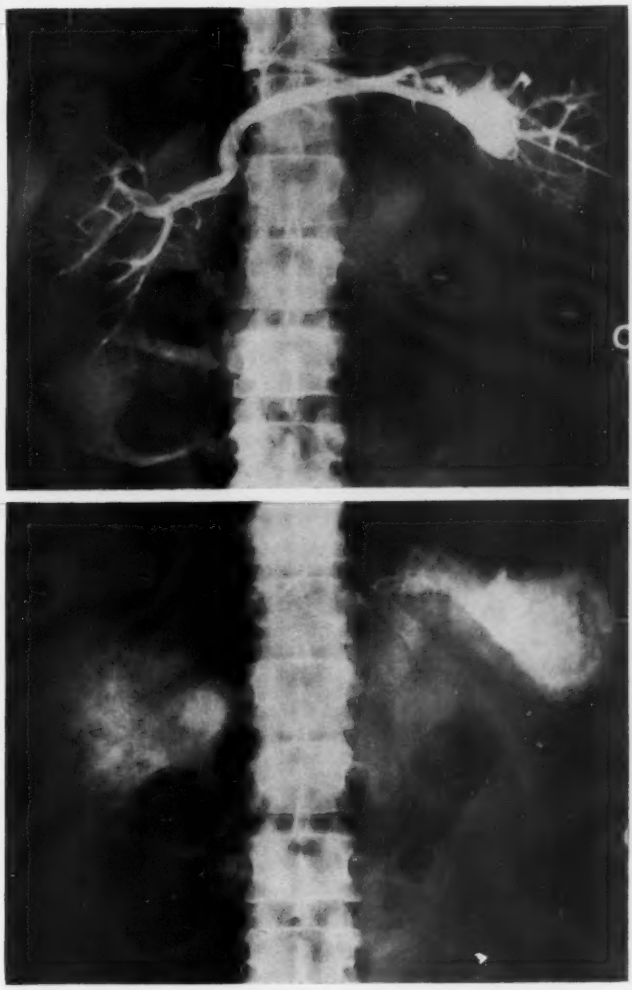


FIG. 10. Transhepatic venography. The contrast medium was inadvertently injected into the left lobe of the liver instead of the spleen. A. (*above*) Early film. The intrahepatic vasculature is displaced superiorly by a carcinoma in the body and tail of the pancreas. A hepatic vein is seen crossing D-11. B. (*below*) Hepatogram phase, showing a large avascular area to the right of D-12. This proved to be a metastatic nodule.

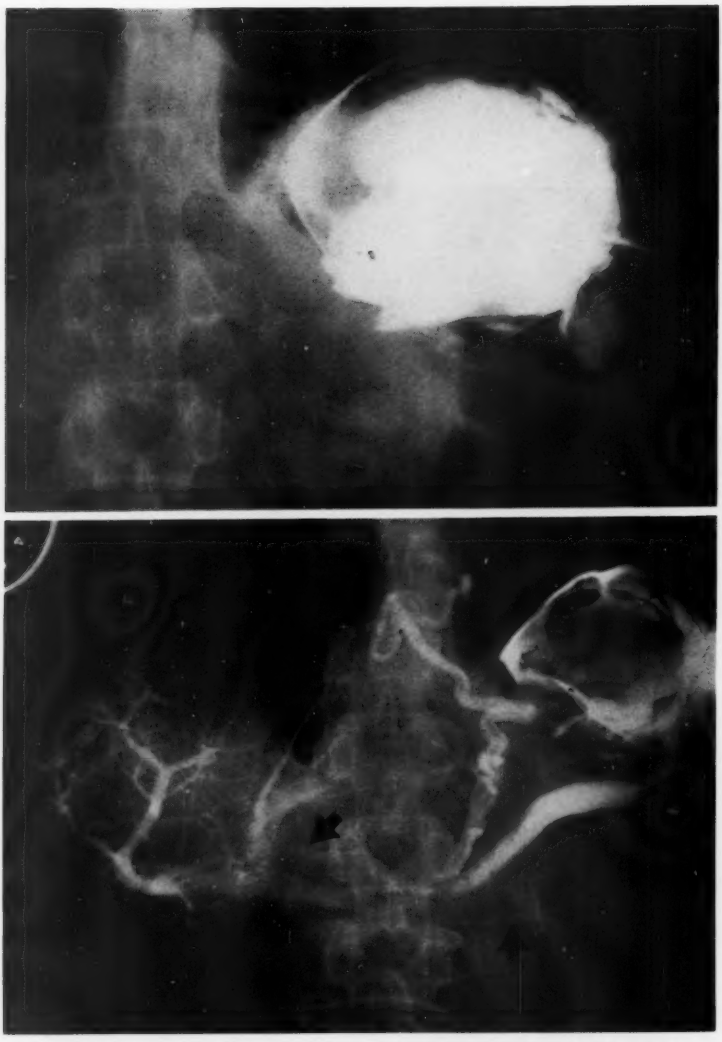
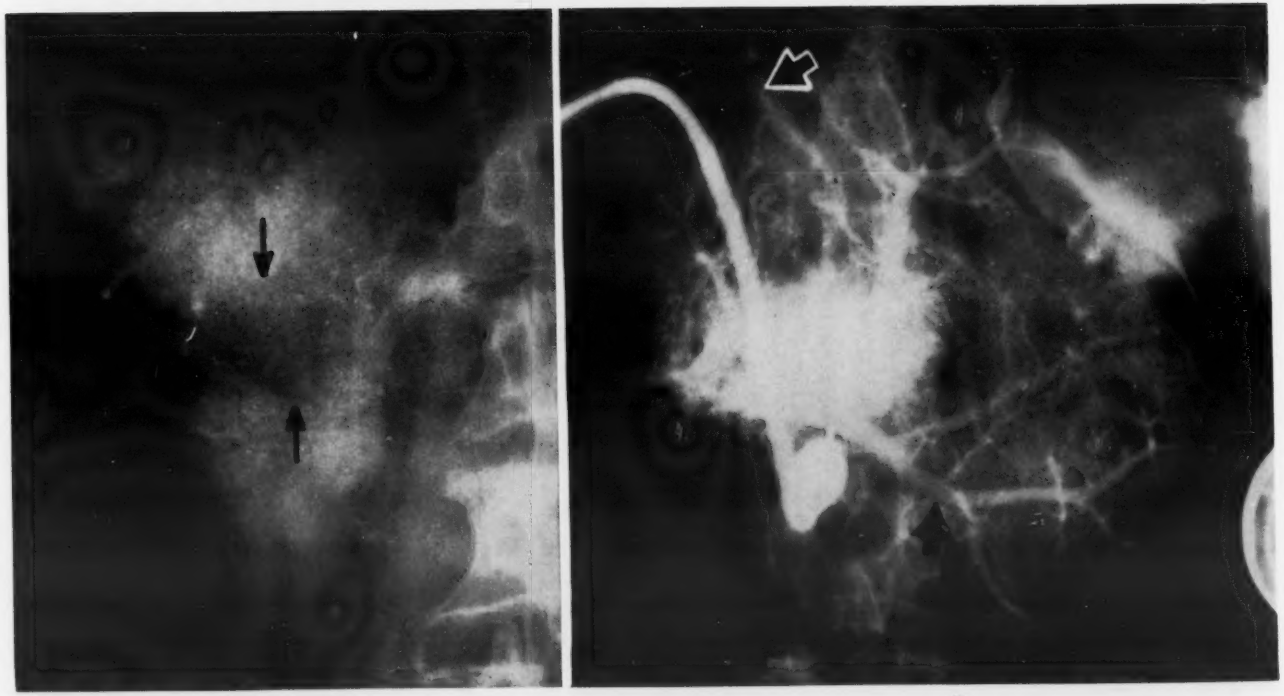


FIG. 11. Male, age 62, with posthepatitic cirrhosis and chronic hepatitis. A large, soft nodule was felt in the epigastrium. A. (*above*) Initial study is unsatisfactory because the contrast medium has been injected into an unsuspected splenic cyst. B. (*below*) Repeat splenoportogram. Splenic pressure, 25 cm. The splenic cyst is well outlined. Inferior displacement of a portal radicle (arrows) supplying the left lobe of the liver.

Because of this fortuitously successful result of transhepatic venography, three additional patients were studied by this technic. In two cases of metastatic liver disease a right-sided intercostal approach was used. Local displacement of intrahepatic vessels by tumor nodules was demonstrated in



C D

FIG. 11C. Hepatogram shows avascular area in right lobe of liver (arrows). D. Percutaneous transhepatic injection into the palpable nodule. Inferior displacement and spreading of portal branches to left lobe are again noted (lower arrow). Hepatic vein filling (upper arrow). Operation revealed only regenerative liver nodules.

both instances. In one of them, contrast material leaked into the peritoneal cavity, outlining metastatic nodules on the surface of the liver. This examination was attended by severe abdominal pain of several minutes' duration, but no other sequelae. In the third patient a percutaneous injection was made directly into a clinically palpable subcutaneous liver nodule, but no definite conclusions could be drawn (figure 11D). In the four cases, visualization of segments of both the portal and hepatic venous systems was obtained. In three, the liver was subsequently examined (one at autopsy, two at operation), and no evidence of liver injury attributable to the procedure was apparent.

Discussion

Percutaneous splenoportal venography with intrasplenic pressure determination has been shown to be a reasonably safe and effective method for the investigation of the portal venous system. Its use need not be confined

Table 2

Correlation Between Hematemesis and Intrasplenic Pressure in 25 Patients with Proved Hepatic Cirrhosis

Intrasplenic Pressure in cm. Saline Solution	Hematemesis	No Hematemesis
Under 20		3
20–25	1	5
25.1–30	3	1
30.1–35	4	1
35.1–40	4	1
40.1–45	1	
60.1–65	1	
Total	14	11
Average pressure	35.4	24.8

The difference is significant ($p < 0.01$).

to the immediate preoperative period, as significant hemorrhage seldom ensues. Puncture of the normal sized or small spleen is moderately difficult, and should be deferred until experience is gained with puncture of the enlarged spleen. Serial films, while not absolutely essential, are certainly desirable, and facilitate interpretation.

In the patients with cirrhosis there appeared to be no close correlation between the roentgenologic extent of the collateral circulation and such factors as the clinical signs, the liver function tests or even the intrasplenic pressure. However, in this cirrhotic group the pressures were significantly greater in those with a history of hematemesis than in those without (table 2). Too few cases of ascites were studied to warrant comment regarding its relationship to intrasplenic pressure. Others have shown that in the presence of ascites the intrasplenic pressure is increased and, parenthetically, the width of the portal and splenic veins is increased to a lesser extent with portal hypertension when there is ascites.[9, 10] There was excellent correlation between the splenic pressures obtained at splenoportography and the portal or omental vein pressures at operation.

In 11 cases, barium swallow failed to reveal the gastric or esophageal varices shown subsequently on the splenoportogram. While the reverse occurred in one case, this patient showed other collateral channels on the splenoportogram, and the splenic pressure was elevated. In the patient with obstruction of the superior vena cava, the esophagram demonstrated varices but the splenoportogram and the intrasplenic pressure were normal. This is not unexpected, for the esophageal venous flow in this condition is in the normal hepatopetal direction.

Thus, percutaneous splenoportal venography proved to be more reliable in the diagnosis of varices than did the barium swallow,[16, 17, 18, 41] and even when splenoportography actually failed to demonstrate the varices, their presence was implied when other collateral vessels filled. Of further interest was the fact that splenoportography revealed gastric varices more often than esophageal varices, although in many cases both were seen.

Our observations indicate that a normal splenoportogram may be encountered in the presence of portal hypertension, and that, conversely, normal intrasplenic pressure may be associated with abnormal collateral circulation. This has been recognized by other writers.[16, 18] These inconsistencies are uncommon, however, and generally the two go hand in hand. Of course, cirrhosis need not be accompanied by either portal hypertension or an abnormal splenoportogram. The rate of injection of the contrast material did not appear to influence the results obtained. This has also been shown experimentally.[10]

Although a mottled appearance of the liver on the hepatogram is sometimes seen in portal cirrhosis,[9, 11, 15, 20] most of our cases failed to show this pattern. Solitary or multiple neoplastic deposits may be evident on the hepatogram, but this appearance is not pathognomonic, and we have been misled by it on several occasions. Similar defects have been reported in cases of amebic abscess,[42] cyst,[21, 28] cirrhosis [15] and hemangioma [27] of the liver. It is also probable that hematoma and other benign, space-occupying lesions would produce them as well.

As is evident from our own experience and that of others, failure of the contrast medium to enter the portal venous ramifications in the liver, or even to fill the extrahepatic portion of the portal vein, does not necessarily indicate extrahepatic block.[10, 18, 23, 33, 43] Apparently the resistance in the liver may reverse the flow in the portal or splenic veins, so that the contrast-laden blood by-passes the liver via the coronary and mesenteric veins and other collaterals. Even when an occlusion of the portal vein is found, it is not always at the site demonstrated by splenoportography.[10] On patients in whom the roentgen findings suggest extrahepatic block, it is advisable at the time of operation to perform a portal venogram,[14, 33] or to obtain verification by taking pressure readings on both the splenic and the hepatic sides of the presumed occlusion. Correlation between the intrasplenic and hepatic vein wedged pressures would serve the same purpose.[17, 44]

Following a successful portacaval shunt, the intrasplenic pressure falls significantly and the venogram may no longer demonstrate collateral flow. In this series, studies made as early as from four to nine weeks postoperatively in three patients showed normal pressures. Splenoportography obtained in one of these three cases showed an adequate anastomosis without collateral veins. It is believed that significant improvement may appear even earlier than this, but in individual cases it may require a much longer period of time.[45, 46]

The accidental injection of the liver during an attempted percutaneous splenic puncture has led us to perform transhepatic venography in three additional patients. Bierman and Steinbach et al. utilized this technic in 1952 and 1953.[47, 48] The method, with detailed observations, has been rereported by Nuñez et al.[49] and Bierman et al.[50] Reliable pressure readings of both the portal and the hepatic venous systems of the liver and differential contrast visualization of these two circulations were obtained. Transhepatic venography was employed for the diagnosis of tumors of the liver and thrombosis of the hepatic vein (Chiari's syndrome).[49] The procedure may also prove useful in studying patients who have had a previous splenectomy. The method merits further evaluation.

Summary

Percutaneous splenoportal venography appears to be a safe and effective method for the study of the portal venous system. Intrasplenic pressure readings obtained during this procedure are a reliable measure of portal venous pressure, and provide additional important information concerning the status of the portal system.

The results of 50 attempts at percutaneous splenoportal venography in 41 patients are reported, 84% having been successful. Splenoportography provides valuable information obtainable in no other manner. Technic, indications, contraindications and complications are discussed.

The method of percutaneous transhepatic venography and its applications are discussed and examples illustrated.

Acknowledgment

We are indebted to Dr. Yoichi Oikawa and Dr. Max Traub, who performed some of the splenograms and assisted with others.

Summario in Interlingua

Inter novembre 1956 e maio 1958, cinquanta percutanee venogrammas splenoportal con determination del pression intrasplenic esseva essayate in 41 patientes de etates de inter tres e 77 annos. Octo esseva non-successos, sed in le majoritate de iste casos, re-examines subsequente succedeva. Venographia percutanee splenoportal se ha provate adequatemente salve e efficace como methodo de investigation del systema porto-venose. Illo produce importante informationes que non es obtenibile in ulle altere maniera. Es discutite le technica, le indicationes, le contraindicationes, le complicationes, e le resultatos.

Venographia percutanee splenoportal es specialmente utile pro determinar le grado de patentia del venas splenic e portal ante un operation e pro evalutar le efficacia del anastomose portocaval post le operation. Le hepatogramma, observate in pelliculas subsequente, pote suggerer le existentia de diffuse fibrosis hepatic o de un tumor intrahepatic, sed le signos es inconstante e a vices deceptive. Venographia percutanee splenoportal pote esser usate a bon profito in le studio de tumores supero-abdominal e etiam in le elucidation de splenomegalia de etiologia indeterminate. In un caso, le methodo serviva a demonstrar un cyste intrasplenic.

In cirrhosis hepatic il non pare exister un stricte correlation inter le extension roentgenologic del circulation collateral e factores como le signos clinic, le resultatos de tests del function hepatic, o mesmo le nivello del pression intrasplenic. Tamen, le pressiones esseva significativemente plus alte in subjectos con un historia de hematemesis que in subjectos sin un tal. Esseva notate un excellente correlation inter le valores pro le pression intrasplenic obtenite per splenoportographia e le pressiones portal o omental trovate al operation. Splenoportographia percutanee se provava plus fidel in le diagnose de varices gastro-esophagee que le inglutition de barium.

Un splenoportogramma normal pote incontrar se in le presentia de hypertension portal e, inversemente, normalitate del pression intrasplenic pote esser associate con anormalitate del circulation collateral. Le rapiditate del injection del substantia de contrasto non pare influentiar le resultatos obtenite. Pelliculas serial, ben que non indispensabile, es certo desirabile. Illos rende le interpretation plus facile. Si le substantia de contrasto non entra in le hepate, il non seque necessarimente que il existe un bloco extrahepatic. In le caso de patientes in qui le constatationes roentgenoscopic suggere le existentia de un bloco extrahepatic, il es a recommendar obtener un venogramma portal al tempore del operation o verificar le suspicion per determinationes del pression a ambe lateres del presumite occlusion.

In tres patientes additional, le injection accidental de substantia de contrasto a in le hepate durante le essayo de effectuar un percutanee punctura splenic presentava le opportunitate de effectuar venographia transhepatic. Visualisation de segmentos del systemas venose tanto portal como etiam hepatic esseva obtenite, e lor displaciamento per nodulos de tumor hepatic esseva demonstrate. Es discutite le methodo del venographia transhepatic percutanee insimul con su applicationes. Exemplos illustrative es presentate.

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THE PLACE OF CORTICOTROPIN IN THE TREATMENT OF MYASTHENIA GRAVIS *

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Opinion differs greatly on the value of corticotropin in treating myasthenia gravis. A review in 1955 [1] shows reports in the literature of only 50 cases so treated, with 25 markedly improved. Despite this seemingly good average, there are few new reports. The large medical centers to which greater numbers of these patients gravitate have tried corticotropin on only a few.

The use of corticotropin in myasthenia gravis was first considered when various investigators reported in 1943 that either corticotropin or adrenal cortex extracts would cause involution of the thymus and other lymphoid tissues.[2, 3] On the basis of these findings, plus their own observation of the increase of synthesis of acetylcholine in brain tissue when corticotropin was given, Torda and Wolff reasoned in 1944 that myasthenia gravis might be benefited by the use of the hormone.[4] They used the crude extracts available at the time on one patient, but never reported their findings. A group working at Mount Sinai Hospital in New York [5] first reported marked benefit in one patient who had myasthenia gravis and a thymic tumor. Shortly afterward Torda and Wolff reported five patients in whom improvement occurred,[6] later expanding this to 15 cases, of whom 10 showed marked improvement and four only slight benefit, while one died during treatment.[7] Schlezinger [8] treated 10 myasthenics in a similar manner and found that all improved, though five of these later relapsed. He felt that the results of retreatment did not equal those of the first treatment. One patient was brought out of a relapse by corticotropin on four occasions, but finally succumbed to the disease.

The experience of Grob and Harvey in 1952 [9] has been especially influential in casting doubt on the usefulness of corticotropin in this disease. They found no improvement whatever in 10 patients, several becoming and staying worse after treatment. Since this report, I have seen no further large series of cases in the literature. Osserman, in his book, *Myasthenia Gravis,* gives the current opinion that ACTH is too dangerous for the treatment of myasthenia gravis.[10] Scattered reports of a few cases, however, continue to imply some benefit.[11, 12]

The present writer has followed six patients with myasthenia gravis, treated by the method of Torda and Wolff. Some of those receiving benefit were treated repeatedly. The results should be of some interest and I hope will stimulate further trial of corticotropin in selected cases.

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Method

One hundred units of corticotropin were given daily for five days. Fifty units of the gel were injected twice daily to some patients. However, if there was any difficulty in breathing or swallowing, the aqueous form was injected so that the effect of the hormone could be halted quickly if the symptoms became alarming. The patients were observed several times daily.

Neostigmine was administered during the period of treatment, usually in the same dose as before. It was common to find that this dose had to be lowered toward the end of this period because abdominal cramps or bradycardia developed.

A low sodium diet was prescribed in all cases, and 2 or 3 gm. of potassium chloride were given daily. These measures seemed to decrease the extreme weakness which often developed during treatment.

The degree of muscular involvement was measured by observing the ease of dressing, swallowing, breathing, and using eating utensils; by noting the degree of ptosis and facial mobility, and by paying strict attention to the patient's assessment of his strength, because lesser changes in muscle fatigue can be felt but not observed.

Results

Six patients have been treated. Of these, five were definitely improved by the treatment; one was not affected at all. Four of those who were helped initially have been treated many times since, with benefit every time. The duration and degree of benefit varied in the different patients and in the different courses of treatment of each patient.

The sequence of events was similar in all of those who received benefit. For the first few days there was a feeling of slightly increased strength. During the last three days and for a day after the last dose the myasthenic symptoms became progressively worse. Occasionally they became severe enough to require suspension of treatment before the planned course was completed.

About three days after the last dose of corticotropin a considerable diuresis appeared, accompanied by increasing strength, which became maximal on the seventh day. Intolerance developed to the large doses of neostigmine. In the next few weeks this increased muscular power waned somewhat, but did not return to its former low level for a period of at least several months, and often for as long as a year.

Blood counts taken during treatment showed a considerable polymorphonuclear leukocytosis, quite commonly around 20,000 white cells, with 90% polymorphonuclear leukocytes.

The usual complications of corticotropin therapy, such as activation of ulcer symptoms and emotional reactions, were observed but were not a serious problem.

Case Reports

Case 1. A 62 year old male machinist had complained of drooping eyelids and double vision for three years. In addition, he had felt generally weak, having had difficulty tying his shoelaces and buttoning his clothes for about a year. After having been diagnosed as having myasthenia gravis, he took neostigmine tablets, 90 mg. daily, with relief of symptoms. However, his underlying condition seemed to be getting worse, and he was faced with the prospect of having to give up his employment.

The patient had had acute nephrolithiasis three years before he was first admitted. An x-ray taken in 1950 had shown marked cervical arthritis, with compression of the trachea by hypertrophic lipping of the bodies of C3 and C4. Though he had been a heavy drinker in his early years, he now drank only two glasses of beer daily.

When admitted to the Samaritan Hospital on May 9, 1953, the patient had marked ptosis of both eyelids, worse on the right. His voice was rather thick, and he had apparent difficulty swallowing his food. The peripheral muscles seemed to have good power, but they fatigued readily with repetitive use. Intramuscular injection of 1 mg. of neostigmine resulted in marked improvement of the ptosis and general muscular fatigability. A loose cough was present, and coarse rhonchi were heard over both lung fields. Otherwise the physical examination was negative.

The urine showed five red blood cells and five white blood cells per high power field. On May 11 the hemoglobin was 16.0 gm. and the leukocyte count was 10,350, with 89% neutrophils and 11% lymphocytes. Chest x-rays, with special attention to the mediastinum, showed no abnormality.

Aqueous corticotropin was started on May 9, 25 mg. every six hours. The patient was also given potassium chloride and a low salt diet. No neostigmine was given at first. For the next two days he was up and about, feeling slightly better than usual. On May 13 he began to complain of difficult breathing and a "choked-up feeling." Neostigmine injections were given, with rapid relief, but symptoms tended to recur. The corticotropin, given for only four days, was discontinued after one especially alarming spell of dyspnea. Difficult swallowing and breathing continued for two days, after which the patient felt well enough to leave the hospital.

One week later he visited my office. He felt much improved generally; ptosis was minimal, and completely disappeared after administration of neostigmine. He had been forced to cut his previous dose of 90 mg. of neostigmine to 45 mg. daily because of abdominal cramps.

When I saw him a few months later he had gradually developed considerable ptosis again. However, he was working, and said his general strength was still much better than before the use of corticotropin.

He continued in this moderate but—to him—satisfactory state until, in February, 1956, he had pneumonia. He responded well to antibiotics given at home, but after convalescence his strength did not return. Once again he had severe ptosis, diplopia, buckling of his knees, and difficulty in handling small objects and in swallowing. He was at first loath to repeat treatment with corticotropin because of the respiratory difficulty during the first course of treatment. Because working seemed impossible, he had me fill out papers applying for social security retirement benefits. Finally, however, six weeks after recovery from pneumonia, he consented to be treated again at the Samaritan Hospital.

Examination at this second admission (March 14, 1956) revealed findings almost identical to those of the first admission. The patient was again started on aqueous corticotropin, 25 mg. every six hours, but this time was given oral neostigmine in addition to the low salt diet and potassium chloride. Treatment was continued for four and one-half days, after which he was allowed to go home at once, still feeling very weak.

He had promised a follow-up visit, but I did not see him until four weeks later. He was back at work and said he felt better than at any time for several years.

He continued at work and felt well until April, 1957, when again his eye symptoms gradually became very troublesome. On this third admission (May 15, 1957), the gel of corticotropin was used for five days, 50 mg. twice daily. Again he improved as before, the improvement becoming maximal a week after the last dose.

For two years after this third treatment with corticotropin I saw him at very infrequent intervals. He continued to work as a machinist the first year, then was forced to retire because of his age. In the second year his myasthenic symptoms became gradually worse. On July 7, 1959, he appeared at my office with complete ptosis of his left eyelid. The left eye did not move synchronously with the right eye. His voice was thick and somewhat nasal, and he seemed to have difficulty in coughing. He consented with misgivings to a fourth treatment with corticotropin.

He was admitted to the Samaritan Hospital on July 7, 1959. Corticotropin was started at once, together with a low sodium, high potassium diet and 45 mg. of neostigmine daily. A blood count the next morning showed a hemoglobin of 17.2 gm. and a white blood cell count of 9,000, with 85% polymorphonuclear leukocytes. After three and one-half days of treatment he began to complain of choking and difficult breathing. Corticotropin injections were then halted. Despite this, general weakness and difficult breathing became worse, and did not respond well to larger and larger doses of neostigmine. On the evening of July 12, extreme general weakness and cyanosis were present, and the patient was placed in a respirator. No cholinergic medications were administered for 12 hours. After that, neostigmine was given, with a prompt response, and he was able to get out of the respirator. His recovery after that was gradual, but when he left the hospital (July 17) he was stronger than on admission, and had only slight ptosis. A follow-up visit three weeks later found him feeling very strong, with no diplopia, ptosis, or difficulty in swallowing or breathing.

Comment: This man responded well to four different courses of corticotropin. The treatment improved him enough to keep him at his job and to alleviate the painful exhaustion which is typical of myasthenia gravis. The crises that occurred during the first and fourth treatments illustrate the type of thing which must be anticipated and either prevented or treated before it has gone too far in those with bulbar symptoms. In these cases with respiratory symptoms, the aqueous form of corticotropin is preferred, since its action is more readily halted than is that of the gel.

Case 2. This 29 year old housewife was admitted to the Samaritan Hospital on May 24, 1953. Eleven years before she had had a gradual onset of double vision, facial muscle weakness, and difficulty in walking that produced a waddling gait. As time went on her symptoms were alternately worse and better. She was now six months pregnant, and her symptoms were much more severe than ever before. She had been using oral neostigmine for years (225 mg. daily), without which she could not get about at all, every muscle in her body seeming to be exhausted.

Physical examination on admission showed a sad, expressionless face, right eyelid ptosed, eyes asynchronous in degree of movement. There was rapid fatigability of every muscle tested, especially the neck and leg groups. After neostigmine orally the patient improved moderately, as shown by functional tests.

Laboratory tests showed the urine to contain a trace of albumin. On May 25, the hemoglobin was 10.7 gm. and the leukocyte count was 14,200, with 81% neutrophils (3% bands) and 19% lymphocytes.

Aqueous corticotropin, begun May 24, was continued for a full five days, 25 mg.

every six hours. Potassium chloride and a low salt diet were ordered, and the patient was allowed to take her own neostigmine at the bedside. During the entire course of treatment she felt no difference in her strength. She left the hospital at the termination of her course of corticotropin. Three weeks later her condition was unchanged and she was still taking the same dose of neostigmine.

After delivery of her child she did not have her hoped-for remission. About a year after the first course of corticotropin, when she was living some distance from Troy, we arranged to have her local physician supervise another course of treatment. This, too, had no effect on her.

Comment: This was the only failure in the present series. Clinically, this patient was not different from the others in physical findings or response to neostigmine. Her lack of improvement after corticotropin could perhaps have been predicted when she failed to get worse during the period of treatment.

Case 3. A 69 year old widow had onset of ptosis and eye muscle fatigue about three months before her admission for treatment on March 8, 1954. She next began to have such difficulty with chewing that she had to assist her jaw with her hand. Her neck became so weak that she could not hold her head up very long. She also felt weak and tired from head to foot. Her oculist had diagnosed myasthenia gravis. She had not yet had a trial of neostigmine.

The past history included diabetes, diagnosed in 1952, well controlled by diet alone. The patient had had several spells of mental depression, from which she recovered after several months of electroconvulsive or institutional treatment. She felt that she might be heading for another depressed spell because of her muscular weakness.

On examination she was noted to have slight ptosis, worse on the right. Blood pressure was 160/94 mm. of Hg. The facial muscles were relatively immobile, and there was apparent difficulty in holding the head erect. When chewing, she assisted jaw movements with her hand. All muscle groups examined showed weakness or rapid fatigability.

On October 9. the patient was given an intravenous injection of 1 c.c. of Tensilon. Within a few moments her ptosis and facial immobility had disappeared. She was enthusiastic about the immediate general increase in strength, which, however, decreased to its previous state in about five minutes. Neostigmine was then given orally, 45 mg. daily, with some improvement.

Laboratory results during the patient's stay were as follows: blood sugar, 181 mg.%; nonprotein nitrogen, 31.5 mg.%; hemoglobin, 14.7 gm.; leukocytes, 13,150, with 63 polymorphonuclear leukocytes, three eosinophils, four monocytes and 30 lymphocytes. Urine showed 1 plus glucose. A Wassermann test was negative. Chest x-ray showed a moderate elevation of the right diaphragm.

Aqueous corticotropin treatment was begun on October 22, 1954, and continued for a full five days, 100 mg. daily. During the period of treatment, and for two days afterward, the patient became progressively weaker, though she had no marked difficulty in swallowing or breathing. On the fourth day after the last dose she noticed a return of her strength, so that when she left the hospital nine days later she no longer had the weakness of neck or jaw which had been her most uncomfortable symptoms. She still had a slight ptosis. Her general strength was much better than it had been for some time, and her mental outlook was much improved.

After discharge this patient was observed at monthly intervals. In a few weeks her general strength receded somewhat, but she no longer had trouble chewing or holding up her head. In April, 1955, her depression returned. Various sedatives

and mood-elevating medications were tried, but she finally was referred to a psychiatric institution for treatment. Among her medications there she was given a good dose of cortisone for a considerable period. She stated that, although her physical condition remained unchanged, her mental outlook improved.

The myasthenic symptoms remained comfortably moderate until August, 1956, when she began again to complain of severe ptosis and difficulty in holding her head erect. She was readmitted to the Samaritan Hospital, received five days treatment with corticotropin gel, 50 mg. every 12 hours, and once again went through the usual sequence of events resulting in disappearance of the neck symptoms and modification of the general weakness and ptosis. Following this she was once again comfortable, got about wherever she wished, and took only 22.5 mg. of neostigmine daily.

In May, 1958, the patient was again uncomfortably aware of facial and eyelid weakness, despite a 90 mg. daily dose of neostigmine. In addition, she now had an anginal syndrome, and complained of severe pain in the hips and legs, which seemed to be due to poor arterial supply. Admitted to the Samaritan Hospital on May 20, 1958, she was given corticotropin for only two days (100 mg. daily). The rest of her two weeks in the hospital was spent in a diagnostic and therapeutic study of her circulatory difficulties. After the first week she noted a marked improvement in her myasthenic symptoms. However, her anginal symptoms did not improve, and she developed a melancholy reaction which required psychiatric attention for a considerable period of time.

In May, 1959, while recuperating from a fracture of the tibia, she complained of general weakness, diplopia and increased ptosis. Corticotropin was administered for three days, in the usual dose of 100 mg. daily. The resultant return of strength has been satisfactory through the time of her last examination, in August, 1959.

Comment: In this patient, corticotropin caused a satisfactory remission lasting several years. When symptoms recurred, re-treatment was equally satisfactory on three occasions.

Case 4. This 45 year old nursing supervisor started with pain in the neck, back and legs seven years before admission. She also had marked general muscular weakness and drooping of the eyelids. She consulted various physicians for her eyes, an orthopedic surgeon for her backache, and another for her legs. Treatment did not help. In November, 1954, after a "virus infection," and at the time of some emotional strain, she developed pain and stiffness of the neck, inability to use her legs, and extreme weakness of her arms. Neurologic examination showed an awkward gait, bilateral knee clonus, hyperactive knee jerks and ankle jerks, and weakness of the legs. Though she was seen by various consultants, no definite diagnosis was made because of the bizarre picture. She gradually improved until she was able to go back to work, her final presumptive diagnosis being toxic neuritis. At work she was very awkward, walking in a waddling manner, having great difficulty arising after kneeling, requiring help with some of her buttons, having trouble using kitchen utensils, and suffering with diplopia and tiring of her eyes.

When the patient was referred to me in January, 1956, an intravenous dose of Tensilon was given with considerable diffidence, because of the unusual picture. She responded promptly with a marked increase in strength. Thereafter she was started on oral neostigmine, 45 mg. daily at first, increasing to 150 mg. For a while she substituted Mestinon, but eventually decided to use neostigmine, which she found more easily adjustable to her daily variations. Even with this large dose of neostigmine she still had a great deal of disability, and agreed to undergo a trial of corticotropin.

On admission to the Samaritan Hospital on February 18, 1956, the above history was obtained. The patient also gave a history of severe hypertension for over 20 years. She had had albuminuria for about the same period of time, with hydronephrosis of the right kidney on pyelography. A total hysterectomy had been performed in 1942 because of adhesions. She was suspected of having purpura hemorrhagica when she bled excessively after tonsillectomy in 1953.

Laboratory findings were: urine, 1 plus albumin; specific gravity, 1.020; hemoglobin, 15.2 gm.; leukocytes, 11,350, with 77% polymorphonuclear leukocytes, three eosinophils, 18 lymphocytes and two monocytes. Platelets were 228,000 per cubic millimeter; nonprotein nitrogen, 31 mg.%; creatinine, 1.3 mg.%. On the third day of corticotropin therapy the leukocytes were 19,000, with 92% polymorphonuclear leukocytes, 7% lymphocytes and 1 monocyte.

Physical examination showed a tall, thin, rather tense woman of 45. Her blood pressure was 200/120 mm. of Hg. The ocular fundi showed somewhat tortuous arteries, with A-V nicking. Reflexes were bilaterally exaggerated. Unsustained clonus was elicited on the right. There was rapid fatigability of all muscle groups, especially apparent in the neck, arms, hands, lower back and legs.

An injection of 1 c.c. of Tensilon intravenously resulted in a prompt increase in strength of all these muscles, though not to normal.

Corticotropin was started, 50 mg. of the gel being given twice daily for two days, and after this the aqueous suspension, 25 mg. four times a day for three days. Potassium chloride and a low salt diet were given, and the patient took her own neostigmine tablets at the bedside. During the corticotropin treatment, and for two days afterwards, she became progressively weaker and stated that she felt "sick." After the last injection she had a diuresis and began to gain in strength. On February 26 she was discharged, feeling much stronger and walking without a waddle for the first time. She had diarrhea that day and had to cut down the dose of neostigmine from 90 mg. to 45 mg. per day.

This patient was followed at weekly intervals as an outpatient. For the first three weeks she proudly showed her new abilities. Then there began a gradual return toward her original level. At this time she was undergoing a considerable emotional upheaval. At the end of two months it was difficult to say that any of her improvement had been retained, though she herself claimed some benefit. Gradually she increased her neostigmine dose until a year after the first treatment she was taking 180 mg. daily.

On January 12, 1957, the patient was re-admitted to the Samaritan Hospital for a second course of corticotropin. The degree of involvement was somewhat greater than on the first admission. She took a full five days of the gel, 100 units daily, potassium chloride and a low salt diet. She felt increasingly weaker until two days after the last dose, when a gradual recovery of strength began, reaching its maximum two weeks later. On the last few days of corticotropin she became very depressed and cried a good deal. At her maximal improvement she was better than after the first course of treatment. Much of this was maintained for three months, and some improvement for one year.

In February, 1958, the patient reported that it was becoming difficult for her to continue her work because of general weakness. She requested re-treatment with corticotropin. Injections were begun as an outpatient on March 13, 1958, and continued for a total of five days after her admission on March 15, 1958. On March 17, 1958, the white blood cell count was 15,200, with 89% polymorphonuclear leukocytes. Because of excessive weakness, the patient remained in the hospital for three days after the last injection. A week later she reported an excellent recovery of her strength. Later she returned to her work, feeling much better.

In June she began to feel increased weakness again, but not enough to interfere with her work.

On August 3, 1958, she telephoned to report the onset of severe headache. She died very suddenly August 4, 1958. Postmortem examination showed a ruptured aneurysm of the circle of Willis. Nothing was found to explain the myasthenia gravis.

Comment: Though this woman had a satisfactory remission after corticotropin on three occasions, the duration of most of this benefit was short. This is frequently one of the most justified criticisms of this treatment. However, it is possible that this response may vary not only in different patients but also in the individual at different times.

Case 5. This 45 year old female factory worker noticed increasing general weakness after a period of arduous double-time work in 1955. First the upper and later the lower extremities became involved. In 1957 she was no longer able to work. In March, 1957, she was started on neostigmine, with moderate improvement. She developed drooping of the right eyelid and protrusion of the right eye in 1958.

Tested at Mount Sinai Hospital in New York City, her protein-bound iodine was reported to be 7; radioactive iodine uptake, 41%. She showed a good response to Tensilon, with a positive ergometer test. When she was given the curare test, with 0.15 c.c. of decubocurarin intravenously, there were a marked increase in weakness and an inability to elevate her extremities. She was then started on Mestinon, which controlled her very well.

When seen by me in May, 1958, she was a slender woman with a noticeable protrusion of the right eye. There was also some drooping of the right eyelid. The thyroid was felt to contain two small, hard nodules. Facial, throat and arm muscles seemed to have good strength, but there was considerable weakness of both shoulders and lower extremities. After administration of Tensilon, these improved.

The patient was admitted for a trial of corticotropin on May 17, 1958. During the five days of administration of 100 mg. daily she became slightly weaker. One week later her muscle strength was considerably improved. I did not see her again, but in mid-June she wrote that she was still feeling stronger than she had in many years. In August a letter from her stated that she was weaker again, and that both eyes were now afflicted with eye-muscle paralysis. In April, 1959, she reported that she was fairly strong, but both eyes were now protruding: "The right eye won't turn to the right and up, the left eye won't turn to the left."

Comment: This woman's illness is myasthenia gravis if we can believe the usually accepted response to cholinergic injection. There are some factors in her findings which make one feel that thyroid dysfunction may also be present. She responded well to corticotropin for several months. The treatment has not yet been repeated because of uncertainty over her exophthalmos.

Case 6. Opinion is divided whether one should include one's experiences with a personal illness in a clinical report. I have decided to do so because I feel I have learned more from my own responses to treatment than I could ever learn from treating others.

My own myasthenia gravis began in 1938. For a few years it was quite severe, but following a tonsillectomy in 1942 it moderated considerably and I was able to resume medical practice. Since then I have been through remissions and recurrences

of ptosis, diplopia, weakness of the hands and general muscular weakness. In December, 1949, in the midst of a severe recurrence which included some difficulty in swallowing, I was given the opportunity to take a five-day trial of corticotropin. I was glad to accept what I considered a rather distant chance for help. In the hands of Torda and Wolff I received corticotropin injections for five days, 100 units daily, becoming much weaker during the course of treatment. One week later I was better than at any time for many years. This improvement remained maximal for only a few weeks, but was very satisfactory for many months.

In May, 1950, while still somewhat improved, I underwent a second course of treatment at The New York Hospital. The increase of weakness during the treatment was less than the first time, and the level of strength a week later was only slightly more than after the first series.

The above two courses of treatment with corticotropin were reported by Torda and Wolff in their series of 15 cases, previously mentioned.[7] Since that time I have undertaken seven additional courses at the Samaritan Hospital, under the watchful eye of Dr. Hermon Gordinier, at intervals of from one to two years. Treatment has been started only after weeks or months of increasingly disabling symptoms, usually ptosis, diplopia, hand weakness with difficulty in writing, and general weakness. My colleagues, recognizing the objective signs of my increasing fatigability, and having seen me improve rapidly and repeatedly after a short course of treatment, have taken to advising me when it is time to start my injections.

In the earlier years I underwent the five days of injections at the hospital, but with experience I have preferred to take the first two or three days while working, and to enter the hospital only when it becomes difficult to get about. My response to the corticotropin has become predictable. The first two days show no particular change. The next three days, increasing fatigue and weakness develop. The first three days after interruption of treatment the symptoms are maximal, with difficult swallowing and sometimes a slight impairment of breathing, double vision, and difficulty in using the hands for dressing or using utensils. Then comes a period of diuresis and a sense of increasing strength. A week to 10 days after the last dose there is a feeling of full power, the return of abilities that have been lost for years. Two weeks later this maximal strength wanes moderately. Over the next several months the muscle abilities level off to a lesser degree, though they are still quite satisfactory when compared to pretreatment strength. Changes after the sixth month vary, seeming to depend more on the presence of infections and stresses.

Following is an outline of the individual Samaritan Hospital admissions for treatment, with notes on pretreatment and post-treatment condition:

December 26 to 31, 1950: Admitted because of diplopia requiring the wearing of an opaque lens for six weeks. Improvement was satisfactory, and the lens was no longer necessary.

December 23 to 28, 1951: Admitted with increasing weakness, diplopia and ptosis since October. Improvement was excellent and well maintained through the following summer.

December 24 to 27, 1952: Diplopia and fatigue had been present since September, recurring and receding. On December 26 the white blood cell count was 16,350 with 89% polymorphonuclear leukocytes. After treatment, all symptoms were alleviated and professional and personal activities were expanded.

December 20 to 25, 1953: Pretreatment level was better than in previous years, but general fatigability, especially of the hands and eye muscles, was present. December 24, 1953, the white blood cell count was 12,500, with 78% polymorphonuclear leukocytes. Post-treatment response was very good, and was maintained for more than a year.

March 25, 1955: Diplopia and difficulty in writing were interfering with work.

On this occasion, all injections were taken at home. The resultant weakness was slightly worse than usual, but I was able to return to the office in three days. My objectives of increasing my hand strength and eliminating the diplopia were attained and maintained through a difficult two years.

July 12 to 14, 1957: Treatment was started at home because of recurrence of ptosis, diplopia and hand weakness. General weakness became severe enough by the fourth day to seem to require hospital observation. An excellent remission was attained. The general level of strength was higher than ever before, and lasted for two years.

May 30 to June 2, 1959: Following four very busy months, muscular strength was lower than it had been since 1957, intermittent diplopia was troublesome, and it was again difficult to write. In addition, for four or five months frequent premature contractions of the heart had been felt after exertion and when first lying down at night. The usual five-day course of corticotropin was given. On May 31 the white blood cell count was 19,300, with 88% polymorphonuclear leukocytes. On June 2 the white blood cell count was 12,200, with 82% polymorphonuclear leukocytes. An electrocardiogram was normal. A good remission was attained. Now, several months later, there is still a higher level of strength than at any time since the onset of myasthenia gravis. One interesting observation is that there have been no noticeable extrasystoles since this treatment.

Comment: It should be of interest that the response to repeated treatment has remained excellent through 10 years, after nine separate courses of corticotropin. Furthermore, there seems to be a gradual improvement of the general level of strength, which may be coincidental, or may be due to the treatment.

The disappearance of the extrasystoles after the last retreatment deserves special mention. Osserman [10] describes heart muscle changes in myasthenia gravis, often in the form of lymphorrhages. It is possible that some such pathologic change was reversed.

Discussion

The use of corticotropin for treatment of myasthenia gravis has been largely neglected for the last seven years. One reason is that expressed in Osserman's book [10]—that it is considered to be too dangerous. Yet there seems no great reluctance in selected cases to try thymectomy, a procedure which is not entirely without danger. It is my conviction that the use of corticotropin is dangerous chiefly for those patients who already have prominent bulbar symptoms. Most patients with myasthenia gravis are troubled mainly by their eye, face or extremity symptoms. In these, the careful use of corticotropin should present a minimum of danger. For those who have difficulty in swallowing or breathing, the outlook is already grave. If other methods of treatment do not bring on a remission in these cases, it would seem that a calculated risk may be worth while. Whenever the treatment is used—but especially in these cases—the precautions outlined should be taken.

Another opinion impeding the more general use of corticotropin for myasthenia gravis is that any benefit which ensues is of too short duration.

In the cases described there is a good deal of variation in the length of response, but for the most part it has been long enough to be worth while. Usually several months to several years passed before the pretreatment level was again reached. For a patient who does not encounter bulbar symptoms during the treatment, five days of corticotropin injections are a small price to pay for a few months of relative comfort. For one with bulbar symptoms, we must weigh the advantages more carefully against the risks. Then, if corticotropin treatment has been of benefit, it should perhaps be repeated before the condition has deteriorated to the previous state.

The mode of action of corticotropin in this syndrome is not known. The most likely theory is that the action is connected with the well documented lysing effect of corticotropin on lymphoid tissues.[2, 3] At the symposium on blood diseases held at the June, 1959, meeting of the American Medical Association in Atlantic City, Dr. William Dameshek stated that, in his experience, striking, even incredible reductions in lymphoid tissue masses result from massive doses of corticotropin or corticosteroids. The pathologic source of the presumed myoneural juncture toxin in myasthenia gravis is not known, but there is reason to suspect the thymus in some, the muscle lymphorrhages in others.

Other sources of lymphatic tissue may also be suspect. The minor respiratory ailments so often associated with lymphoid hypertrophy are also very often accompanied by increased severity of myasthenia. In my own case, tonsillectomy was followed by a marked moderation of symptoms. One may wonder if the carotid sinus denervation reported by French surgeons [13] may work because of the removal of several cervical lymph nodes during the dissection.

The exacerbation of myoneural paralysis during and shortly after the administration of corticotropin may be postulated to be due to lysis of the pathologic lymphoid masses, with release of toxins into the bloodstream. The polymorphonuclear leukocytosis occurring during the first few days of corticotropin administration may also be a reaction to this lysis of tissue.

In regard to the dose of corticotropin, the amount given seems to be adequate but may not be optimal. A study of different dosages might be worth while.

Summary

1. Five new cases of myasthenia gravis treated with short courses of corticotropin are reported. Four of the five experienced a beneficial response, some of them repeatedly after each course.

2. One case, previously reported, has been re-treated eight more times, with a worth while remission every time.

3. It is suggested that a reëvaluation of corticotropin therapy be made in selected cases, chiefly those without prominent bulbar weakness. It is important that the safeguards outlined be used.

4. It is proposed that not only thymus but also other lymphatic tissues might be the source of the myoneural toxin of myasthenia gravis. Corticotropin may act by causing lysis of these tissues.

Summario in Interlingua

Le opiniones differe con respecto al utilitate de corticotropina in le tractamento de myasthenia grave. Le prime reportos esseva optimistic, sed plus tarde plure autores signalava periculos e reportava manco de successo. Subsequentemente e usque al tempore presente, nulle grande serie de casos tractate con corticotropina ha essite publicate.

In le presente serie, le methodo de Torda e Wolff esseva usate. Usualmente isto consisteva de 100 unitates de corticotropina per die durante cinque dies. In le casos de successo del therapia, le symptomas myasthenic esseva aggravate durante le curso de medication, sed iste phenomeno poteva esser modificate per le administration de chloruro de kalium, un dieta a basse contento de natrium, e neostigmina. Le tractamento deberea esser arrestate si le symptomas respiratori deveni alarmante.

Le presente articulo reporta le casos de cinque patientes con myasthenia grave que esseva tractate in le maniera indicate. In un del casos, nulle beneficio esseva obtenite. Quatro monstrava melioration, comenciante tres dies post le ultime dose, con un maximo post dece dies e un continuation a grados decrescente durante periodos de inter duo menses e plus que un anno. Inter le quatro patientes qui beneficiava, tres recipeva un total de 11 cursos de tractamento, con melioration effectuate in omne caso. Le quarte patiente, con prominente symptomas bulbo-respiratori, esseva tractate a bon successo quatro vices, sed in duo de iste occasiones, un serie paralyse respiratori se disveloppava, e le planate curso esseva interrumpite.

A parte le supra-listate casos, le autor mesme ha myasthenia grave e se ha subjicite in le curso de 10 annos a novem cursos de tractamento a corticotropina. Post cata un del cursos, su condition se ha meliorate promptemente e durante un satisfacente periodo de tempore.

In le discussion de un possibile modo de action del droga, le ben-documentate facto es signalate que corticotropina exerce un effecto lytic super tissu lymphatic tanto normal como etiam anormal. Un augmento de tissu lymphatic in varie organos es le major constatation pathologic in myasthenia grave. Es postulate le possibilitate que tissus lymphoide altere que illo del thymo es le fonte del toxina myoneural de myasthenia grave.

Super le base de iste experientias, le these es presentate que breve cursos de corticotropina pote esser usate con bon successo in multe casos de myasthenia grave, providite que le supra-delineate precautiones es observate. In patientes con prominente symptomas bulbar, le uso del droga—si on vole riscar lo del toto—require le plus meticulose attention.

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THE SIGNIFICANCE OF LATERAL AND GENERALIZED RETINAL SHEEN * †

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Previous publications from this clinic have described a wet, glistening appearance of the entire retina that is frequently associated with toxemia of pregnancy and glomerulonephritis.[1, 2] Since this retinal sheen was not present in normal pregnant patients, in patients with other types of edema, or in patients with chronic hypertensive vascular disease, it was suggested that its recognition might be useful in the diagnosis of toxemia and the differentiation of toxemia from hypertensive vascular disease. Although further experience in a larger series of patients has strengthened these preliminary impressions, such claims have been based on purely subjective experience. No data have been furnished regarding the specificity of generalized retinal sheen for toxemia or its incidence in the normal population, nor has an attempt been made to differentiate generalized retinal sheen from the wet-appearing retinae of normal young patients.

The purpose of this present report is: (1) to define further the sheen of toxemia, presenting data on its specificity, (2) to characterize the wet-appearing retinae of young patients, and (3) to differentiate these normal findings from the abnormal generalized sheen.

Methods and Materials

Part I: Ophthalmoscopic examination was performed on 83 pregnant patients in the Toxemia Clinic of the District of Columbia General Hospital by an ophthalmologist (W. F.) and an internist (F. F.) without knowledge of the patients' histories or physical findings. Pupils were dilated with 10% phenylephrine hydrochloride solution, and the examination was performed

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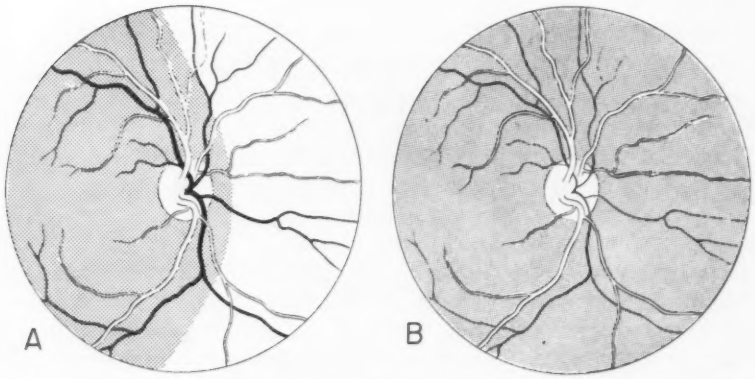


FIG. 1. Diagrammatic representation of normal lateral sheen (A) and abnormal generalized sheen (B). Note that lateral sheen commonly extends past the midline to an area immediately adjacent to the optic disc. Note also the decrease in caliber of retinal arteries (black) when generalized sheen is present.

in a dark-room. Included in the group were 30 patients with unequivocal signs of toxemia, e.g., recent rise in diastolic pressure, edema of the periorbital areas and hands, and albuminuria. The average age of these patients was 18.5 (14 to 24) years.

Although fundus photography has been used routinely in this Clinic to document vascular changes, it has not been successful in documenting retinal sheen. The brightness of the camera light, and the fact that this light focuses on a single area of retina, change the glassy appearance of the sheen to that of a localized exudate similar to the highlights noted in a fresh pathologic specimen when photographed.

Part II: To evaluate the wet-appearing retina of the young normal patient, ophthalmoscopic examination was performed independently through dilated pupils by three different investigators on 294 nonpregnant patients

TABLE 1

Ophthalmoscopic Findings in 262 Normal Patients

Age	Number of Patients	Sex		Lateral Sheen				Medial Extent			Type of Distribution	
		Male	Female	Not Present	Mild	Moderate	Severe	Less than 1 Disc Diameter	More than 1 Disc Diameter	More than 2 Disc Diameter	Only Along Vessels	Generalized
Under 20 yrs.	64	7	57	0	44	13	7	39	19	6	23	41
21–19 yrs.	80	9	71	0	75	2	3	48	27	5	21	49
30–42 yrs.	56	30	26	14	32	9	1	39	3	0	30	12
Over 40 yrs.	62	54	8	60	2	0	0	0	0	0	2	0

without obvious cardiovascular disease. These patients were chosen from the Medical Wards of the District of Columbia General Hospital. The findings were recorded independently on mimeographed report forms. Each investigator was asked to record whether sheen was present or not, its location (whether lateral, medial or generalized, using the optic disc as the dividing line between lateral and medial), its intensity, and whether generalized over the entire retina or particularly along the course of the blood vessels; and, finally, the state of the retinal arteries, whether in spasm or not.

One hundred seventeen patients were female, 177 were male; 82 were white and 212 were Negro. Seventy-six patients were under 20 years of age, 95 were between 21 and 29 years, 59 were between 30 and 40 years, and 64 were over 40 years of age.

Because of its fluid-like appearance and resemblance ophthalmoscopically to the generalized sheen of toxemia, which is influenced by diuretic therapy, 34 patients with a severe degree of lateral sheen were administered chlorothiazide in a dosage of 1 gm. a day for seven days. The degree of the intensity of lateral sheen before and after chlorothiazide was determined independently by three investigators.

Results

Part I: When ophthalmoscopic examination was performed without knowledge of the patient's history or other physical findings, neither investigator recorded generalized retinal sheen or spasm of the retinal arteries in any of the 53 "normal" pregnant patients. In the 30 patients with unequivocal signs of toxemia, both examiners agreed that generalized retinal sheen and spasm of the retinal arteries were present in 23 patients, and that only lateral sheen and no retinal artery spasm was present in two patients (figure 1). The findings in the remaining five patients varied. One investigator noted generalized sheen without vasospasm in three patients, and sheen of the lateral portion of the retina plus retinal artery spasm in two patients. The other investigator noted generalized sheen plus no spasm in two patients, and lateral sheen plus spasm in three patients.

Part II: There was no agreement in the ophthalmoscopic findings of the three individual investigators in 32 of the 294 patients examined. In the remaining 262 patients there was uniform agreement among the three investigators. The results in these patients are recorded in table 1. It can be noted that sheen was present in the lateral portion of the retinae in all patients under 29 years of age, both male and female. In 129 of the 144 patients the sheen was mild, in 15, moderately severe, and in 10, severe. It should be noted that although the sheen extended past the midline over to the medial side of the retinae in all patients, it was noted more than 2 disc diameters on the medial side in only 11 patients (figure 2). Sheen was not seen in any patient more than 3 disc diameters medially.

In the group under 20 years of age the sheen was located predominantly

along the course of the vessels in 23 instances, while in 41 patients it did not particularly follow the blood vessels. In the group between 21 and 29 years of age the sheen followed the course of the vessels in 21 patients, and was more or less generalized in distribution in the lateral portion of the retina in 49 patients.

Fourteen of the patients in the 30-to-40 year old group showed no retinal sheen at all. Six of these were male and eight were female. Of the remaining patients, 32 showed evidence of mild lateral sheen and nine showed moderate sheen. Although the predominantly lateral sheen extended to the area immediately adjacent to the disc on the medial side in all of the 42 patients, in only three did the sheen extend more than 1 disc diameter on

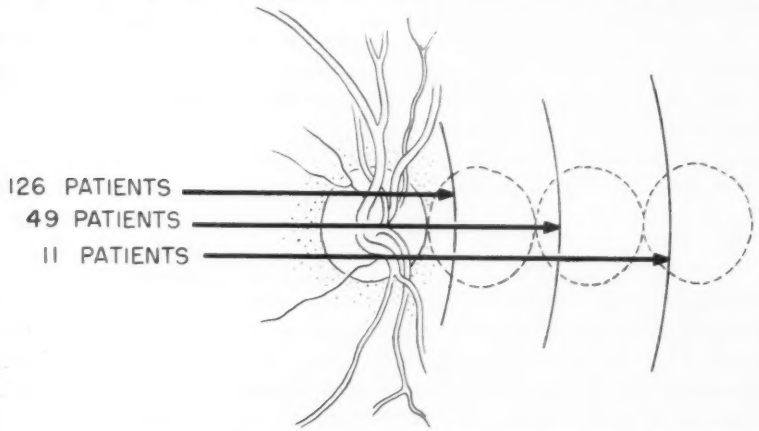


FIG. 2. Medial extent of lateral sheen in 262 patients without cardiovascular disease. In 76 patients, lateral sheen did not cross the midline.

the medial side. The sheen was visualized best along the course of the blood vessels in 30 cases, whereas there was no particular relation to the vessels in 12 patients.

Minimal sheen of the lateral portion of the retina was visualized in only two patients in the group over 40 years of age. The ages of these patients were 41 and 42 years, respectively.

Despite a weight loss of at least two and one-half pounds in each patient, only four patients treated with chlorothiazide demonstrated a slight decrease in the intensity of lateral sheen. It would therefore seem that, unlike the generalized sheen of toxemia and glomerulonephritis, lateral retinal sheen does not represent retinal edema.

DISCUSSION

The findings of the two investigators who performed ophthalmoscopic examination on the 83 pregnant patients without knowledge of their histories

or other physical findings lend credence to the preliminary observation that generalized retinal sheen is frequently associated with toxemia. Since neither investigator found generalized sheen in any of the 53 pregnant patients without disease, it would also seem that this finding is not present in the normal population. The personal experience of one of us (F. F.), who has found generalized retinal sheen in only seven of 3,559 young patients without toxemia or glomerulonephritis, further attests to the specificity of generalized retinal sheen.

The generalized sheen of toxemia is promptly decreased following diuretic therapy. It is not uncommon, for example, to see in a patient with toxemia of pregnancy a severe degree of generalized retinal sheen completely disappear in 12 hours following diuresis, leaving a normal amount of lateral sheen. This evidence therefore suggests that the generalized sheen of toxemia represents superficial retinal edema.

Previous publications from this clinic have not stressed the importance of spasm of the retinal arteries in toxemia and glomerulonephritis.[1, 2] Generalized reduction in the caliber of retinal arteries which produce threadlike arteries seems more common in these conditions than does segmental spasm of arteries which produce sausage-type arteries. Instead of the ratio of vein to artery being 3 : 2 or 4 : 3, the generalized reduction in caliber of the arteries commonly changes the ratio to 4 : 1 or 5 : 1. Like others,[3] we have observed complete spastic obliteration of the retinal arteries associated with transitory blindness in acute toxemia and glomerulonephritis, with the return of patency of the arteries and the restoration of vision when the vasospasm is decreased.

It is interesting to note that, from the pathophysiologic standpoint, toxemia of pregnancy is characterized by sodium retention and generalized vasoconstriction, and that both of these phenomena can be visualized ophthalmoscopically. Generalized retinal sheen and a decrease in caliber of the retinal arteries characterize toxemia. These same ophthalmoscopic findings are also present in patients with acute glomerulonephritis. The recent renal biopsy studies in patients with toxemia of pregnancy which have shown membranous glomerulonephritis [4] may account for the similarity in ophthalmoscopic findings. From these and other studies,[5] we feel that the retinal circulation closely reflects the renal circulation, and we agree fully with Elwyn [6] that angiospastic retinitis characterizes acute renal disease.

Studies are now in progress in this clinic to establish the frequency of both generalized retinal sheen and retinal arterial spasm in glomerulonephritis. Data thus far have led us to the impression that, although retinal arterial spasm seems to be as pronounced in glomerulonephritis as in toxemia, generalized retinal sheen seems to be less prominent and more transitory than in toxemia. Perhaps the sodium retention which normally accompanies pregnancy accounts for the greater degree of generalized sheen in toxemia.

The ophthalmoscopic findings in the 262 patients without obvious disease demonstrate that a wet, glistening appearance of the lateral portion of the

retina is a completely normal finding in the majority of patients under 40 years of age. The intensity and area of distribution of this lateral sheen seem to be related to age: the younger the patient, the more pronounced and widespread the sheen; the older the patient, the less pronounced and more localized the sheen. The lateral portion of the retina seems to be covered by a thin film of fluid (very similar in appearance to generalized sheen of toxemia) which overlies and partially obscures the retinal vessels. Although this lateral sheen frequently extends past the midline over to the medial side (using the optic disc as the dividing line between lateral and medial), it is seldom noted more than 1 disc diameter on the medial side (figure 2). This lateral sheen is most pronounced around the macular area, and frequently seems to follow the course of the blood vessels on the lateral side of the retina.

Such a glistening, metallic reflex of the retinae of young normal patients has been described by Goodside,[7] who referred to it as the anterior (internal) limiting membrane. Salzmann [8] has defined this structure as a glassy membrane of 1 to 2 mμ. in thickness, showing on surface view the impression of basal cones of Müller's fibers as irregular polygonal fields. Although it is well defined, no attempt has been made to localize the anterior limiting membrane predominantly to the lateral or medial side of the retina.

The reason for the rather abrupt decrease in the intensity of these lateral retinal reflexes following age 40 is not clear. Friedenwald [9] has found a decrease in the stainability of the anterior limiting membrane with age. Similarly, Dimmer [10] has suggested that a chemical change occurring in the anterior limiting membrane with age may be accompanied by a physical alteration in the mirroring quality of the membrane. He suggests that the refractive index of the retina diminishes, and that the vitreous increases with age, thus producing a diminution in the quantity of regularly reflected light.

No explanation can be given for the variations in the intensity of lateral sheen in patients of the same age group. It does not seem to be particularly related to sex or race, although only 82 of the 294 patients studied were white. Similarly, the lack of response to chlorothiazide therapy would seem to indicate that lateral sheen is not related to sodium retention. The refractive status of the eye must influence the brightness of these reflexes. Goodside [7] has shown that the hyperopic eye shows much brighter reflexes than does its myopic opposite number. He suggests that the tenseness of the anterior limiting membrane, and thereby its physical characteristic as a reflecting surface, is more favorable in the hyperope than in the myope.

The usually sharp line of demarcation between the wet-looking lateral portion of the retina and the dry-appearing medial portion makes differentiation between lateral and generalized sheen obvious. Occasionally, however, lateral sheen may extend over to the medial side, making it difficult to distinguish it from generalized sheen by ophthalmoscopic appearance alone. As mentioned above, any area of dryness on the medial side of the retina

excludes generalized sheen. The presence or absence of retinal arterial spasm also helps greatly in differentiating the normal from the abnormal. Generalized sheen plus retinal arterial spasm is abnormal; lateral sheen plus no arterial retinal spasm is normal.

Summary

Generalized retinal sheen is a wet, glistening appearance of the entire retina, including the nasal field, which is frequently associated with toxemia of pregnancy and glomerulonephritis. It is seldom seen in the normal population. It is almost always associated with retinal arterial spasm, which helps greatly in differentiating it from lateral retinal sheen. Its prompt decrease or disappearance following diuretic therapy suggests that it represents retinal edema.

Lateral sheen is a wet, shiny appearance of the lateral portion of the retina seen in the normal population under 40 years of age. This glistening appearance is more intense around the macula. Although it frequently extends just beyond the midline, its medial extent is seldom more than 1 disc diameter. The younger the patient, the more intense and greater its area of distribution. Although wet in appearance, lateral sheen probably does not represent retinal edema, since it is not influenced by diuretic therapy. It probably represents the anterior limiting membrane of the retina.

Summario in Interlingua

Ben que previe studios ab iste clinica ha reportate le association de un apparentia humide e satinate del integre retina con toxemia de pregnantia e glomerulonephritis acute, usque nunc nulle datos specific ha essite publicate con respecto al specificitate o al etiologia de ille phenomeno o al aspectos in que iste relucentia del retina differe ab le apparentia humide del retinas de juvene patientes normal. Un examine ophthalmoscopic esseva effectuate independentemente in 83 patientes pregnante per duo investigatores qui non esseva al currente del historias del patientes o del constatationes facite in le examine physic de illas. Le gruppo includeva 30 patientes con signos inequivoc de toxemia. Ni le un ni le altere del investigatores trovava un relucentia generalisate in le 53 gravidas normal. Ben que le duo investigatores non esseva de accordo in lor constatationes in cinque patientes con toxemia, ambes notava un generalisate relucentia del retina in 23 alteres.

Pro evalutar le retinas de juvene patientes, examines ophthalmoscopic esseva effectuate independentemente in 294 patientes de ambe sexos per tres investigatores. Nulle relucentia del typo generalisate esseva trovate in ulle del patientes. Un relucentia del portion lateral del retina—con le disco optic como linea de separation—esseva notate in omne le 144 subjectos de minus que 29 annos de etate, in 42 del 56 de etates de inter 30 e 40 annos, e in duo del 62 de etates de plus que 40 annos. Ben que therapia a chlorothiazida reduceva promptemente le generalisate relucentia retinal de toxemia, illo habeva nulle effecto super le relucentia lateral.

Il pare justificate concluder (1) que le generalisate relucentia retinal es un anormalitate que occurre in association con toxemia de pregnantia e representa probabilemente un manifestation de edema retinal e (2) que le relucentia lateral es normal in patientes de etates de minus que 40 annos.

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BRUCELLOSIS: EXPERIENCES WITH 224 PATIENTS *

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Knowledge of the diseases of man and animals which are grouped under the heading of "brucellosis" has increased considerably since the initial studies of Bruce. Bacteremic brucellosis has received much attention,[18, 21, 22] but other types of brucellar infections have not been studied so extensively. Selected observations by members of our group concerning patients with brucellosis have been reported from time to time.[1, 3, 6, 8–10, 13, 15, 16, 20, 23] The present report represents a study of 224 patients examined at the Mayo Clinic during the 19-year period 1940 through 1958. Our classification of the various types of the disease is presented in table 1.

Bacteriologic Considerations

Cultures for Brucella organisms were made by inoculating hormone-blood agar in Petri dishes with specimens of blood or tissue and incubating the preparations in 10% carbon dioxide, as required by *Brucella abortus* species. Fluids such as blood were cultured in bottles containing trypticase soy agar and broth in an atmosphere of carbon dioxide, as described by Castaneda and associates.[2] The organisms were tentatively designated as being of the genus Brucella if they were small, coccobacillary, gram-negative, nonmotile rods which produced urease and (with the exception of *Brucella melitensis*) hydrogen sulfide. Such designation was accepted if the organisms did not ferment sugars or produce indole, and were agglutinated to full titer by known stock-specific Brucella antiserum. Material cultured for Brucella organisms in most instances was cultured also for tubercle bacilli, fungi, and more common organisms such as streptococci and Salmonella.

Distribution of Patients

According to Bacteriologic Data: In table 2, patients from whom brucellar organisms were isolated are divided into two groups: (1) those from whom brucellar organisms were obtained by culture of a specimen of blood, and (2) those from whom brucellar organisms were obtained by culture of specimens of specific tissues. When it was not possible to obtain cultural

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TABLE 1

Brucellosis: Classification

Type*	Onset	Systemic Manifestations	Cultures	Agglutination Titer	Remarks
Bacteremic	Usually acute	Usually severe; without remission	Positive (blood)	High and rising	In past, rare instances wherein positive cultures persisted after symptoms subsided
Serologic	Acute or subacute	Same as bacteremic	Negative	Same as bacteremic	Only positive finding is high agglutination which is not specific. Special evaluation required. May result from premature therapy
Localized	Possible history of acute episode; frequently insidious	Usually absent; rarely recurrent for years	Positive (tissues)	Infrequently high; usually low or absent	Local lesion, low agglutination, prolonged duration with remissions may distinguish from "serologic" type. Best classify as "serologic" if cannot obtain cultural proof from apparent localization

* Mixed type: When the characteristics of the disease place it in an indeterminate area among the above types.

confirmation of the disease (serologic type), the patients concerned were also divided into two groups: (1) those who gave antibrucellar agglutination titers of 1:1,280 or more, and (2) those who gave agglutination titers of 1:200 to 1:800. An additional group of 49 patients who gave agglutination titers of 1:200 or higher was excluded from the study, since the evidence of active brucellosis in them was equivocal.

Brucella organisms were produced by culture of the blood of 47 patients on one or more occasions. All of these 47 patients gave agglutination titers in excess of 1:200 at some time during their illness. *Brucella abortus* was cultured from the blood of 20 patients, *Brucella suis* from five patients, and *Brucella melitensis* from four patients. The species of Brucella was not determined in 18 patients.

Brucella organisms were obtained from 36 patients by culture of specimens taken for biopsy or aspirations of specific tissues. The agglutination titers of these patients ranged from absence of agglutination to titers of more than 1:1,600. However, in most instances the titer did not exceed 1:200. The organisms cultured from these localized lesions are listed in table 3. Most of the localized lesions were caused by *B. suis*.

Eighty-one patients with the signs and symptoms of brucellosis yielded an antibrucellar agglutination titer of 1:1,280 or more, but Brucella organisms could not be obtained from them by culture. Some of these patients,

TABLE 2

Summary: All Cases

Brucellosis, Type		Cases, No.
Culturally proved:	(a) bacteremic	47
	(b) localized	42
Culturally unproved (serologic and mixed types) with agglutination titers of:	(a) 1:1,280 or more	81
	(b) 1:200 to 1:800	54
Total		224

TABLE 3

Strain of Brucella and Source of Culture in 42 Patients with Culturally Proved Localized Brucellosis

Culture, Source	Brucella, Species			
	abortus	suis	melitensis	Undetermined
Bone or bone marrow		3	1	3
Joints and spinal column	6	3	1	
Soft tissue (including lymph node)		3	1	1
Prepatellar bursa	2	1		
Spleen		3	1	1
Liver		1		
Genitourinary tract		4	1	2
Lung		4		
Totals	8	22	5	7

who were classified as having evidence of serologic or mixed brucellosis, had received suppressive forms of therapy administered elsewhere prior to the time our diagnostic studies were carried out. Others in this group probably had localized brucellosis, but because of the inaccessibility of the lesion, satisfactory tissue for culture was unobtainable. For example, four patients had high agglutination titers, a history very suggestive of a previous episode of acute brucellosis and roentgenologic evidence of spondylitis, but tissue satisfactory for culture could not be obtained from them. To avoid nosologic difficulties, we have classified patients such as these four as having either serologic or mixed brucellosis, but conceivably they could be considered to have culturally unproved localized brucellosis. As implied in table 1, however, we restricted the term, "localized brucellosis," to those instances where Brucella organisms actually have been grown from specific tissues.

Fifty-four patients also classified as having serologic or mixed brucellosis yielded antibrucellar agglutination titers ranging from 1:200 to 1:800. They comprise the last group in table 2. Possible reasons for our inability to obtain cultural proof of the disease in these patients are the same as those as

TABLE 4

Distribution of Patients According to Occupation

Occupations	Culturally Proved Brucellosis		Agglutination Titer (Serologic and Mixed Types; No Cultural Proof)	
	Bacteremic (47 Patients)	Localized (42 Patients)	1:1,280 or More (81 Patients)	1:200–1:800 (54 Patients)
Farming	19	20	48	28
Butchering or meat packing	4	6		3
Creamery worker	2			
Stock buyer		2		
Veterinarian	3		3	2
Other	19	14	30	17

given for members of the preceding group. However, many of these patients had rising agglutination titers, an observation which was interpreted as corroborating the diagnosis.

According to Occupation and Sex: In table 4 it is apparent that, of the patients with bacteremic brucellosis, more than one-half were farmers or persons otherwise occupied with animal husbandry. Among the 47 patients with bacteremic brucellosis there were 44 males and three females.

A similar incidence according to sex occurred in 42 patients with localized brucellosis, since of such patients there were 41 males and one female. Among these patients, farming also represented the largest occupational group.

TABLE 5

Distribution of Patients According to Selected Clinical Features

Symptom or Sign	Culturally Proved Brucellosis		Agglutination Titer (Serologic and Mixed Types; No Cultural Proof)	
	Bacteremic (47 Patients)	Localized (42 Patients)	1:1,280 or More (81 Patients)	1:200–1:800 (54 Patients)
Fever	43	14	75	34
Chills	27	6	42	20
Sweats	17	6	29	15
Fatigue	15	9	39	25
Weakness	17	8	9	20
Loss of weight	14	7	19	14
Splenomegaly	11	7	12	3
Backache	10	1	7	7
Adenopathy	4	7	15	6
Hepatomegaly	4	5	6	1
Rigidity of neck	3	0	1	0

The same conclusions as the foregoing, regarding the incidences of sex and occupation, were roughly true of these incidences among the victims of serologic and mixed brucellosis.

According to Symptomatology: The symptoms and signs noted most frequently are listed in table 5. An attempt has been made to correlate the frequency of these with the bacteriologic data. Fever and chills occurred in many of the patients with bacteremic brucellosis. Other common complaints were sweats, fatigue, weakness and loss of weight. Enlargement of the spleen was the physical abnormality most frequently detected. Adenopathy and hepatomegaly were noted in a few patients.

In contradistinction to what was true of patients with bacteremia, fever was noted in less than half of the patients with localized brucellosis. Weakness and loss of weight were mentioned by a few. Recurrent systemic symptoms were noted in some, but in most, complaints, when present, were restricted to the organs or systems involved. Physical findings, if present, also were usually indicative of the site of involvement; for example, an enlarged spleen was palpated occasionally, or swelling and tenderness of a joint were noted. In some instances, however, no distinct physical findings could

TABLE 6

Distribution of Patients According to Duration of Illness Prior to Diagnosis

Illness, Duration	Culturally Proved Brucellosis		Agglutination Titer (Serologic and Mixed Types; No Cultural Proof)	
	Bacteremic (47 Patients)	Localized (42 Patients)	1:1,280 or More (81 Patients)	1:200–1:800 (54 Patients)
Less than one year	27	16	42	28
More than one year	2	14	14	14
Indeterminate	18	12	25	12

be attributed to the diseased organ. Thus, in one patient renal granulomatous brucellosis was detected during an entirely unrelated surgical procedure. In some patients with localized brucellosis in the lung, the only evidence of abnormality was an asymptomatic nodule detected in a roentgenogram of the thorax.

Some of the patients who had the signs and symptoms of active brucellosis with high agglutination titers, but from whom cultural proof could not be obtained, had been ill for only a short time. In contradistinction, at least 14 of these patients had had symptoms compatible with a brucellar infection for more than a year prior to the time the agglutination titers were obtained (table 6).

The clinical findings in the 54 patients who had signs and symptoms compatible with active brucellosis whose agglutination titers ranged between 1:200 and 1:800, but also from whom no cultural proof could be obtained, were quite variable, since again, both acute and more prolonged forms of the disease are represented in this group (table 5). Fever and chills occurred primarily in those patients with acute serologic brucellosis, but a few of the patients with the mixed type who had had symptoms for more than a year had fever of significant degree.

TABLE 7

Summary of Selected Laboratory Data

	Culturally Proved Brucellosis		Agglutination Titer (Serologic and Mixed Types; No Cultural Proof)	
	Bacteremic (47 Patients)	Localized (42 Patients)	1:1,280 or More (81 Patients)	1:200–1:800 (54 Patients)
Leukopenia	18	3	13	8
Leukocytosis	2	4	8	4
Normal leukocyte count*	27	35	60	42
Sedimentation rate over 20 mm. (Westergren)	10	10	31	20
Anemia†	3	7	1	3

* This means that the number of leukocytes was greater than 4,000 and less than 10,000 per cubic millimeter of blood.

† This means a concentration of hemoglobin of less than 12 gm. per 100 ml. of blood in men or less than 11 gm. in women.

According to Hematologic Data: Some selected hematologic data are seen in table 7. Leukocyte counts in most of the patients with either bacteremic or serologic brucellosis ranged between 4,000 and 10,000 per cubic millimeter of blood. Leukopenia was present in an appreciable number of patients (18), but leukocytosis was rare. A sedimentation rate of more than 20 mm. in one hour by the Westergren method was present in less than a fourth of the patients in whom this test was conducted.

The lack of abnormal hematologic data in the majority of patients with localized brucellosis is apparent in the table.

Comment

Brucellosis in the central portion of the United States is to a great extent an occupational disease, as is apparent from the incidence according to sex and occupation among our 224 patients with the disease. We have found it convenient to classify the disease according to the following types (table 1).

First is the *bacteremic* type, in which the essential characteristic is the culture of Brucella organisms from specimens of blood; in such patients, agglutination titers are usually high and frequently rising; victims of this type of the disease generally are acutely and severely ill.

The second type is *serologic,* in which the essential characteristic is detection of a high agglutination titer in a patient with systemic manifestations compatible with the disease, from whom it is not possible to produce Brucella organisms by culture of specimens of blood, and in whom there is no local lesion to examine histologically and bacteriologically.

The third type is *localized,* in which the essential characteristic is the growing of Brucella organisms from specific tissues of the victim, such as the lung, spleen, kidney and so on; in these patients the process may have been present many years, often is relatively asymptomatic, but rarely is productive of recurrent systemic manifestations; agglutination titers as a rule are low or absent; results of cultures of specimens of blood are negative.

A fourth type is *mixed* in which the characteristics of the disease place it in an indeterminate area among the preceding types. This type is exemplified by the patient having bacteremic brucellosis and simultaneous culturally proved localized brucellosis. The mixed type also includes such conditions as skeletal lesions from which Brucella organisms are not grown, but in which serums demonstrated a high agglutination titer.

The fact that nearly all of our patients who had bacteremia were males is of interest, since there was a predominance of females over males in the total registration at the Mayo Clinic during the period surveyed. That direct contact with infected animals, and especially the products of conception of such animals, is responsible for the majority of brucellar infections, rather than ingestion of contaminated milk products, is perhaps suggested by the fact that most of our patients were engaged in occupations related to animal

husbandry. Most of the infections studied by us were caused by *B. abortus* or *B. suis,* and only a few were caused by *B. melitensis.*

The majority of the patients with bacteremic brucellosis had oral temperatures in excess of 100° F. at some time during their illness. However, in the years before adequate treatment was available, several patients were seen whose symptoms and signs, including fever, completely subsided but whose blood would produce positive results of culture for several months thereafter.

Follow-up information revealed that the vast majority of the patients with bacteremia had recovered in less than a year. A few of those not receiving what is now considered to represent adequate antibacterial therapy had symptoms which appeared to be related to their acute illness for more than a year after the onset of the disease. In none of the patients with bacteremic brucellosis regarding whom follow-up information was obtained did clinical manifestations of localized lesions develop. Absence of such manifestations may be due to the fact that a high proportion of these patients received treatment with antibiotic or chemotherapeutic drugs which may have successfully suppressed further growth of the Brucella organisms. Furthermore, *B. suis,* the type most likely to cause localized lesions, was specifically identified in only five of the patients who had bacteremia.

In our classification (table 1) there is no reference to "chronic brucellosis," since it appears that the condition of many victims of emotional, rather than brucellar, disease has been so classified, with consequent confusion. On the other hand, chronic localized brucellosis, in which lesions arise in such tissues as bones, lymph nodes and the lung, from which brucellar organisms can be grown, is a clinical entity. As a rule, chronic localized brucellosis is not associated with marked systemic reaction, but rarely a patient is encountered in whom severe constitutional manifestations may recur for years prior to isolation of the organism from various tissues.[16, 20] Four of the patients who had culturally proved localized brucellosis were entirely asymptomatic at the time of diagnosis. These were the patients with localized granulomatous lesions in the lungs which were detected entirely in routine roentgenograms. Preoperatively, the surgeon may be unaware of the nature of other localized lesions, notably those of the skeletal system, and hence his securing of material for culture often is of extreme value. Spondylitis, in which brucellar organisms invade an intervertebral disc, is the most usual type of such skeletal involvement. Bones such as the humerus, femur, skull and ribs sometimes are affected; suppurative arthritis is not common,[23] but prepatellar bursitis is not infrequent. The gall-bladder, liver, spleen, popliteal aneurysm and kidneys also may become foci of chronic brucellar infection, and Brucella organisms have been recovered from such tissues removed at operations.

All of the patients with bacteremic brucellosis had agglutination titers in excess of 1:200 at some time during their illness (table 8). This is a

closer correlation between bacteremic brucellosis and significant agglutination titers than has been reported by others. Taylor and associates found that 2% of the patients they studied gave negative reactions,[22] and Castaneda and co-workers reported the incidence of negative reactions to be 12% in their series of 100 patients.[2]

The agglutination titers of the patients with culturally proved localized infections also were of interest. No agglutination was detected in the serum of six patients, and the agglutination titers in the serum of most patients in this group were low (table 8). This may have been due to the fact that most of the localized lesions were well encapsulated, thus keeping the antigen from the general circulation. It has been said that agglutination may be demonstrated after incubation of such nonreactive serums with phenol-killed Brucella organisms, thereby removing "blocking antibodies." [24]

TABLE 8

Summary of Agglutination Titers in Culturally Proved Infections

Agglutination Titer	Brucellosis	
	Bacteremic (47 Patients)	Localized (42 Patients)
1:1,280 or more	32	2
1:800	7	4
1:600	3	2
1:400	4	5
1:200	1	9
1:100	0	8
1:16 through 1:80	0	6
Negative	0	6

Although brucellosis is diagnosed with certainty only by cultivation of brucellar organisms from specimens of the patient's blood, body fluids, excreta or tissues, the agglutination test is of great value. The limitations of the agglutination test include these:

1. Vaccination against cholera, use of brucellergin, and the occurrence of tularemia may induce antibrucellar agglutinins.

2. An incorrect diagnosis may be made in a patient with an unrelated disease who has a residual agglutination titer from previous brucellosis.

3. Serum of patients with chronic localized lesions from which brucellar organisms have been isolated may give negative agglutination reactions.

It appears inadvisable to make a diagnosis of brucellosis unless (1) brucellar organisms have been produced by culture, or (2) brucellar agglutinins are present in high or increasing titer in patients strongly suspected clinically of having the infection. We do not employ skin testing in patients suspected of having brucellosis because, in our hands, positive results of such tests cannot be correlated well with the disease, and also because the ability of such tests to induce antibrucellar agglutinins can prove confusing.

Sadusk and co-workers [19] have emphasized that *B. abortus* strain 19 can at times cause serious infection in man. In one of our patients, a veterinarian, who had the bacteremic form of the disease, the infection may have been caused by this strain.

Endocarditis is a complication which has been a cause of death in patients with brucellosis.[5] The possibility that aortic stenosis may originate on the basis of brucellar endocarditis has been raised.[17] Call and associates [1] have reported two cases where bacterial endocarditis was caused by Brucella organisms.

Some of our patients with either acute bacteremic or serologic brucellosis did not receive any type of therapy, but most were treated with various antibiotic agents or combinations of antibiotics. In 1949 Heilman demonstrated that chlortetracycline combined with streptomycin was more effective than was chlortetracycline alone in suppressing the growth of Brucella organisms in mice.[7] Tetracycline, when combined with streptomycin, is as effective in the suppression of the growth of Brucella organisms as is chlortetracycline. In our clinical experience the best results in the treatment of acute bacteremic and serologic brucellosis have been obtained with this same combination of antibiotics (tetracycline and streptomycin).

Herrell and Barber reported the satisfactory results obtained in some of the patients included in our series.[8] Fourteen additional patients with bacteremic brucellosis have been treated with tetracycline combined with streptomycin for a two-week period, and their condition has been followed since treatment for more than two years. In none of these patients has there been evidence of bacteriologic or symptomatic relapse.

Knight,[12] Criscuolo and co-workers,[4] and Magill and Killough,[14] have concluded also that the relapse rates and length of treatment required in brucellosis are significantly reduced if streptomycin is added to a regimen of the tetracyclines. The Joint FAO/WHO Expert Committee on Brucellosis has recommended tetracycline-streptomycin therapy as the antibrucellar regimen of choice.[11]

In the treatment of acute bacteremic and serologic brucellosis we have employed 500 to 750 mg. of tetracycline or one of its analogues given orally every six hours, and 1 gm. of a streptomycin agent injected intramuscularly twice daily for two weeks. In the presence of chronic localized brucellosis the amount of streptomycin is reduced to a total of 1 gm. daily, and combined treatment is given for four weeks.

In the dose recommended, streptomycin or dihydrostreptomycin only rarely causes damage to the vestibular or auditory function of the eighth cranial nerve. Since deafness is more serious than impairment of vestibular function, it appears that therapy with streptomycin alone, rather than a combination which includes dihydrostreptomycin, is preferable. Detection of the early vestibular and auditory complications of streptomycin therapy can be effected best if audiometry and vestibular turning tests are carried out periodically during treatment, and again six months after treatment has been discontinued. Cutaneous reactions, although unusual, are more common when streptomycin is used than when the tetracyclines are given.

Precise evaluation of results of antibiotic therapy in our patients with

localized lesions is not possible, since in many of them surgical procedures were carried out in addition to the antibiotic therapy. Among our patients, surgical procedures generally were performed for diagnostic purposes, but occasionally surgery seemed advisable as a therapeutic measure. The latter purpose is accomplished when a site of chronic infection, such as osteomyelitis, must be drained or, more rarely, when an organ is to be removed. In the latter regard, splenectomy rarely has been necessary in instances of hypersplenism manifested by leukopenia, thrombocytopenia or hemolytic anemia. Moreover, in certain patients with splenomegaly who had infection difficult to control medically, splenectomy has been performed.

Summary

Brucellosis in the United States is primarily an occupational disease affecting males. Of 224 patients with brucellosis, more than half were engaged in occupations related to animal husbandry. Most of the patients with bacteremic brucellosis exhibited the clinical manifestations of severe systemic infection. A few patients with localized infections had recurrent constitutional symptoms. Abnormal leukocyte counts or increased erythrocyte sedimentation rates occurred in only a small percentage of the patients. In all patients with bacteremic brucellosis the agglutination titers were 1:200 or more. In the patients with localized brucellosis the agglutination titers often were low or absent. *B. suis* was the strain of Brucella most commonly isolated from the localized lesions. Results of treatment with a combination of tetracycline and streptomycin were satisfactory in patients who had bacteremic brucellosis. Surgical drainage or excision of localized infections was of value in diagnosis and treatment.

Summario in Interlingua

In le Statos Unite, brucellosis es primarimente un morbo occupational que affice le masculos. Inter 224 patientes con brucellosis, plus que un medietate esseva ingagiate in occupationes connectite con le elevation de bestial. Le majoritate del patientes con brucellosis bacteriemic exhibiva le manifestationes clinic de un sever infection systemic. Plure patientes con localisate infectiones habeva recurrente symptomas constitutional. Anormal numerationes leucocytic o acceleration del sedimentation erythrocytic occurreva in solmente un micre procentage del patientes. In omne le patientes con brucellosis bacteriemic, le titros de agglutination esseva 1:200 o plus. In le patientes con brucellosis localisate, le titros de agglutination esseva frequentemente basse o mesmo absente. *Brucella suis* esseva le racia de brucella que esseva isolate le plus communmente ab lesiones localisate. Le resultatos del tractamento con un combination de tetracyclina e streptomycina esseva satisfactori in patientes qui habeva brucellosis bacteriemic. Drainage chirurgic o excision de infectiones localisate esseva de valor in le diagnose e in le tractamento.

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HYPERINSULINISM SECONDARY TO DISEASE OF THE PANCREAS AND ORGANS ADJACENT TO THE PANCREAS: A REVIEW OF THE WORLD LITERATURE*

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Hyperinsulinism is caused by either an insulin-producing tumor of the pancreas or a diffuse hyperplasia of the islands of Langerhans. This paper will deal with the hyperplasia and neoformation of insular tissue occasionally associated with pathologic changes of the glandular portion of the pancreas. While involvement of the endocrine function in pancreatitis is commonly manifested by hyperglycemia, a number of cases have been reported in which hypoglycemia was the presenting symptom. The existence of such a syndrome has not been generally appreciated in this country. A number of reports from abroad and the sparsity of observations of this kind in the English literature have prompted me to collect and review as much information on this entity as was available to me in the world literature of the last 25 years. My interest in this particular syndrome was aroused by the observation of a case I published some time ago.[1] A brief report of this case will illustrate the representative clinical and pathologic findings.

Case Report

A white woman was found to have pulmonary tuberculosis at the age of 30 years. At age 38 she developed severe epigastric pain, and her stool became clay-colored. No jaundice was present. At age 40 she was treated for pyelitis and diabetes mellitus. The fasting blood sugar at that time was 300 mg.%. During the subsequent years her diabetes was only poorly controlled with 120 units of insulin and a diabetic diet containing 60 gm. of carbohydrates, and at age 44 she was hospitalized for diabetic coma. At age 45½ the patient was admitted to the hospital in hypoglycemic coma after she had received her usual 30 units of insulin, followed by her breakfast. She responded promptly to the intravenous injection of dextrose.

Physical examination revealed a poorly nourished woman with advanced pulmonary tuberculosis. Examination of the yellow, copious and foaming stool showed complete absence of pancreatic enzymes. Pancreatic calculi were demonstrated by x-ray. Fasting blood sugar values ranged between 90 mg.% and 135 mg.%, and the urine was free of sugar and acetone, while the patient was on a very liberal diabetic diet and no insulin was given. The glucose tolerance curve remained typical for diabetes, but dropped to hypoglycemic levels four hours after the ingestion of glucose. Injection of 5 units of insulin caused marked hypoglycemia. Three weeks after admission the patient died of the rapidly advancing phthisis.

In addition to a far advanced pulmonary tuberculosis, the autopsy revealed a

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hard, cirrhotic and atrophic pancreas containing numerous calculi. The microscopic examination of the pancreas showed the acinar tissue to be completely replaced by connective tissue. The islands of Langerhans were definitely diminished in number, but the majority of those remaining were markedly enlarged—up to 10 times the size of a normal islet (figure 1). The adrenals were normal.

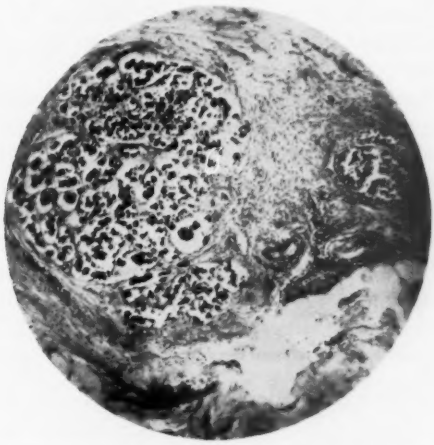


FIG. 1. Cirrhotic pancreas with giant island (left) and normal island of Langerhans (right).

This case illustrates the basic anatomic and functional changes of the islands of Langerhans which were responsible for the disappearance of a previously quite severe diabetes mellitus and the occurrence of episodes of hypoglycemia.

REVIEW OF EXPERIMENTAL STUDIES

It is well known that the islands of Langerhans possess a remarkable ability for compensatory growth and regeneration by way of a hyperplasia of existing islets and the formation of new islands. In animal experiments several investigators [2-4] have found an abundance of healthy islands and a very definite enlargement of the insular apparatus, with a markedly increased insulin content of the pancreas after ligation of the pancreatic duct and secondary necrosis and atrophy of the exocrine portion of the pancreas. These anatomic changes have been referred to in the European literature as the Herxheimer-Mansfeld phenomenon. Severe, even fatal hypoglycemia and increased carbohydrate tolerance were observed in these animals. Friedman and Marble [5] resected all but a small portion of the pancreas in rats and found considerable hyperplasia of the islands several weeks after operation. The smooth contour of the islands was broken up by the extension of masses of insular tissue between the surrounding acini. There was marked hypertrophy of the beta cells, while the alpha cells remained unaltered. Also,

Bencosme and co-workers [6] found neither proliferation nor new formation of the alpha cells in dogs following partial pancreatectomy. The alpha-beta cell ratio is thus often markedly shifted in favor of the latter. Woerner [7] observed an intense compensatory increase in the island tissue, especially of the beta cells, in guinea pigs in which he maintained a moderate increase of the blood sugar by continuous intravenous infusion of dextrose. These findings were similar to those observed after injection of anterior pituitary extracts.

It is beyond the scope of this paper to discuss the extensive histologic studies concerning the mode of neoformation of insular tissue. Suffice it to state that regeneration of the islands is now generally assumed to take place by mitosis of existing islet cells and budding of new endocrine cells from a system of anastomosing small tubules which arise from the larger pancreatic ducts. These ductules are composed of undifferentiated epithelium which, following an injury to the pancreas, can give rise to a few new acini and, to a great extent, to new islands.[8]

Reported Clinical Cases

Nature has duplicated those animal experiments in man under various circumstances. Perusal of the world literature reveals that hyperinsulinism due to hyperplasia and neoformation of the islands of Langerhans has been found under the following conditions:

1. Chronic pancreatitis, including traumatic pancreatitis.
2. Cirrhosis and atrophy of the pancreas due to obstruction of the pancreatic duct by:
   a. Pancreolithiasis.
   b. Cholelithiasis.
   c. Tumor of the head of the pancreas.
   d. Congenital atresia of the pancreatic duct.
3. Lesions of organs adjacent to the pancreas (biliary system, gastrointestinal tract).

Twenty-two cases of histologically proved hyperplasia of the islands of Langerhans were gathered from the world literature and are compiled in table 1. All cases had episodes of more or less severe hypoglycemia. Three patients died in hypoglycemic shock.[18, 22, 24] Nine patients had diabetes mellitus which either improved in the course of the disease or subsided entirely. Several French authors [9, 10, 11] have listed chronic pancreatitis as one of the causes of pancreatogenic hypoglycemia, and have called this entity "pancréatite chronique hypoglycémique." In some of these patients, partial pancreatectomy brought dramatic relief of the hypoglycemic attacks. In their case of pancreolithiasis with hypoglycemia, Leger and his co-workers [16] observed that the "néoformation langerhansienne" was proportional to the

degree of obstruction by calculi and dilatation of the pancreatic ductules. Their patient was also markedly improved by a subtotal pancreatectomy. In a review of six patients who underwent pancreatic surgery for spontaneous hypoglycemia, Becker [12] found two cases of insular adenoma and four cases of chronic pancreatitis with diffuse hypertrophy and hyperplasia of the islands of Langerhans. Differential stains of the alpha and beta cells of the islands in the excised material revealed a shift of the normal alpha-beta cell ratio of 1:4–5 [23, 25] in favor of the beta cells, resulting in ratios from 1:6 to 1:8. The same observation has been made by other investigators.[9, 23]

In most instances it is rather difficult to determine an accurate time relationship between the onset of the pancreatitis and the appearance of spontaneous hypoglycemia. Of interest in this regard is the observation in a case of traumatic pancreatitis in a 40 year old man.[9] A laparotomy done 24 hours following a rather severe trauma to the abdomen showed an edematous and hemorrhagic pancreas. About three months later the patient for the first time experienced a typical hypoglycemic attack, manifested by intense hunger and abundant perspiration, which was promptly relieved by the administration of sugar. Because of repeated episodes of severe hypoglycemia and epigastric pain, a partial pancreatectomy was eventually performed 17 months after the accident. Microscopic examination showed widespread sclerosis of the pancreas and numerous hyperplastic islands of Langerhans along the edge of the pericanalicular fibrosis. These islands were made up almost entirely of beta cells. The pain and hypoglycemia subsided after the operation.

Hyperinsulinism due to hyperplasia and neoformation of insular tissue has been seen in eight cases of obstruction of the external pancreatic secretion by concrements in the common bile duct and tumors of the head or body of the pancreas. Mallet-Guy [18] reported the case of a patient with obstructive jaundice due to a pancreatic tumor who died postoperatively in hypoglycemic coma. The autopsy revealed numerous hyperplastic islands of Langerhans and extensive sclerosis of the pancreas. Another case of fatal hypoglycemia was observed by Tiling [24] in a seven month old girl with congenital atresia of the pancreatic duct.

Hyperplasia of the islands with hyperinsulinism has also been found in patients with extrapancreatic lesions. In a patient with an ulcer on the posterior wall of the stomach who had attacks of rather severe hypoglycemia, a partial pancreatectomy with removal of 28 gm. of pancreatic tissue resulted in a remarkable improvement of the patient.[15] There were no adhesions between the stomach and the pancreas, and no signs of pancreatitis. Microscopic examination of the pancreas revealed a markedly increased number of islets, some of which were hyperplastic. There was no evidence of inflammation. In another patient [19] with cholecystitis and spontaneous hypoglycemia a biopsy of the pancreas also showed an increased number of islands which, however, were of smaller than normal size. No inflammatory

changes were seen. This patient's symptoms could be controlled by diet alone.

Meissner [26] reported 10 cases of cystic pancreatic fibrosis in children with a generalized tendency to neoformation of islands by budding from the cystically dilated ductules and acini. Since there was no evidence of hypoglycemia, these cases have not been included in tables 1 and 2.

TABLE 1

Histologically Proved Cases of Hyperplasia of the Islands of Langerhans, with Hyperinsulinism Secondary to Pancreatic and Extrapancreatic Disease

Author	Chronic Pancreatitis	Pancreolithiasis	Cholelithiasis	Tumor of Pancreas	Atresia of Pancreatic Duct	Extrapancreatic Lesions	Initial Diabetes
Becker[12]	X						
Becker[12]	X						
Becker[12]	X						X
Becker[12]	X						X
Brinck and Sponholz[13]		X					
Burkhardt[14]				X			X
Burkhardt[14]				X			X
Cadenat et al.[9]	X						
Faure-Beaulieu et al.[15]						X	
Friedlander[1]		X					X
Leger et al.[16]		X					
Leriche and Schneider[17]				X			
Leriche and Schneider[17]	X						X
Mallet-Guy[18]				X			
Michaud[19]						X	
Ranström[20]			X				X
Sanes et al.[21]		X					
Sanes et al.[21]		X					X
Schmidt[22]		X					X
Terbrüggen[23]				X			
Terbrüggen[23]				X			
Tiling[24]					X		
22 Cases	6	6	1	6	1	2	9

In addition to the histologically proved cases, a number of similar cases of hyperinsulinism associated with lesions of the pancreas, the gastrointestinal tract and the biliary system have been reported where histologic confirmation of insular hyperplasia was not obtained. Inasmuch as hypoglycemia may result from diverse pathologic conditions, great discretion must be used in attributing hypoglycemic attacks to a hyperfunction of the islands of Langerhans. In this connection, it is worthy of emphasis that hyperinsulinism without any histologic abnormality of the islets has been encountered in some patients who were completely relieved of their hypoglycemic convulsions by a partial pancreatectomy.[27]

A critical perusal of the literature revealed 21 cases having clinically diagnosed pancreatic or extrapancreatic disease associated with hypoglycemia which was attributed to a hyperfunction of the islands of Langerhans. These cases are compiled in table 2. Sixteen out of 21 patients had chronic

pancreatitis or calcifying pancreatitis, one had an adenocarcinoma of the pancreas with obstructive jaundice, and four had extrapancreatic lesions. Of special interest is another case of traumatic pancreatitis, reported by Iberti,[37] that is analogous to the one previously mentioned in that the time interval between the trauma and the appearance of hyperinsulinism was the same in both. This 27 year old male patient underwent a laparotomy following a severe blow to the epigastrium and was found to have acute hemorrhagic pancreatitis with fat necrosis. He made an uneventful recovery, but

TABLE 2

Cases of Hyperinsulinism Associated with Pancreatic and Extrapancreatic Disease, and Attributed to Hyperplasia of the Islands of Langerhans in Which Histologic Confirmation of Hyperplasia Was not Otained

Author	Chronic Pancreatitis	Pancreolithiasis	Cholelithiasis	Tumor of Pancreas	Extrapancreatic Lesions	Initial Diabetes
Becker[12]	X					X
Berardinelli[31]				X		
vanBuchem and van de Griend[32]	X					X
Duesberg and Eickhoff[33]		X				X
Grott[34]	X					
Grott[34]	X					
Grott[34]	X					
Grott[34]	X					
Grott[34]	X					
Harris[35]					X	
Harris[35]	X					
Herrmann and Gius[36]		X				
Iberti[37]	X					
Kämmerer and Michel[28]	X				X	X
Lasch[28]					X	
Lasch[28]	X					
Lasch[28]					X	
Mallet-Guy[18]			X			
Ryan[30]	X					
Ryan[30]	X					
Schermann[40]	X					
21 Cases	14	2	1	1	4	4

three months later developed symptoms and signs of hyperinsulinism. These could be controlled by diet alone, without recourse to surgery. Reporting the occurrence of spontaneous hypoglycemia in three patients with diseases of the upper gastrointestinal tract, probably associated with chronic pancreatitis, Lasch [28] considered hyperinsulinism a "second disease," which often is not given proper attention in the management of these patients. In this respect, it is of interest that hypoglycemia per se has been described as causing rather severe pain and diarrhea. In a survey by Cane [29] of 28 cases of spontaneous hyperinsulinism without evidence of organic disease, 25 patients had "hunger pain," severe abdominal cramps and occasional diarrhea during the hypoglycemic attack.

An additional number of patients with hyperinsulinism and extrapancreatic pathology were observed by Berger.[30] He collected 50 cases with disease of the biliary tract associated with disturbance of the carbohydrate metabolism. Twenty-six of these patients showed evidence of hyperinsulinism, 24 had diabetes mellitus. He also reported several instances of hypoglycemia in diseases of the stomach and duodenum. However, it could not be clearly ascertained how many of these patients also had chronic pancreatitis.

Discussion

The histologic picture common in the cases of hyperinsulinism secondary to chronic pancreatitis as well as to obstruction of the pancreatic duct is that of widespread disintegration of the acinar tissue, which is eventually replaced by fibrosis resulting in extensive sclerosis of the pancreas. In chronic pancreatitis, this end stage is preceded by chronic inflammation and, in the case of pancreatic duct obstruction, by dilatation of the pancreatic canaliculi. The islands of Langerhans, which usually remain fairly intact, may be diminished in number, but some or all of them are enlarged, measuring 500 to 600 microns (normal size 120 microns), and occasionally they reach 10 times the normal size. Small conglomerations of island cells, made up almost completely of beta cells, are often seen budding from the canalicular epithelium.

Several factors probably act as stimuli for the neoformation of islands. In all but five cases, hyperplasia of the islands was preceded by either chronic inflammation and necrosis or atrophy and cirrhosis of the acinar tissue, or both. The greatest number of hyperplastic islets was usually found in that portion of the pancreas which showed the most extensive inflammation or sclerosis. The fact that 28 out of 43 patients had chronic pancreatitis, with or without formation of pancreatic calculi, stresses the importance of inflammation and eventual destruction of the acinar tissue as an etiologic factor in this syndrome. As mentioned above, injury to the pancreas mainly stimulates regeneration of the endocrine cells, and only to a much lesser degree that of the acinar tissue. According to Loubatières and his coworkers,[41] increased pressure in the pancreatic ducts in anesthetized dogs caused a drop in blood sugar, the mechanism of which was obscure. The authors considered the possibility of either a direct excitation of the islands or a reflex action of the islands in response to an irritation of vegetative nerve fibers. This phenomenon may play a contributory role in cases of hyperinsulinism associated with obstruction and dilatation of the pancreatic ducts. Hyperemia of the pancreas due to inflammation of the organ itself or that of adjacent structures might also favor a hyperfunction of the islands.[23] Hyperglycemia has been shown in animal experiments [7] and also in man to be a strong stimulus of the regenerative capability of the islands. Hypertrophy and hyperplasia of the islands of Langerhans in children born

of diabetic mothers are well known. Fatal hypoglycemia occurred in such a child shortly after birth when, with the sudden cessation of the maternal demand for insulin, the hyperplastic islands caused severe insulin shock in the infant.[42] Regeneration of island tissue can be found in many diabetic patients, and remarkable remissions of diabetes mellitus,[43] occasionally even followed by spontaneous hypoglycemia,[44, 45] have been reported.

Spontaneous pancreatogenic hypoglycemia may be due to either organic or stimulative hyperinsulinism.[46] The latter has also been called functional or reactive hyperinsulinism. The majority of the compiled cases in whom fasting blood sugar values or glucose tolerance tests were reported presented the picture of stimulative hyperinsulinism, with normal or sometimes higher-than-normal fasting blood sugar values, and a sharp drop of the blood sugar to hypoglycemic levels three to five hours after the ingestion of dextrose during the glucose tolerance test, or following a meal rich in carbohydrates. Other patients in this series with low fasting blood sugar levels and severe hypoglycemia not relieved by proper diet were accorded the diagnosis of organic hyperinsulinism, and usually required partial pancreatectomy. Some patients exhibited an unusual sensitivity to insulin in that they went into hypoglycemic shock after administration of small amounts (5 to 10 units) of insulin. A similar observation was made in patients with diabetes mellitus secondary to pancreatitis who received insulin.[47] In both instances the loss of glucagon-secreting alpha cells and the resulting failure to mobilize sugar from the body depots in response to the fall of the blood sugar may well have been responsible for this increased insulin sensitivity. Furthermore, the newly formed islands are made up almost exclusively of beta cells. This circumstance most likely causes an increased secretion of insulin in response to the ingestion of carbohydrates and, in the absence of the compensatory action of glucagon, results in reactive or stimulative hyperinsulinism.

Our present knowledge of diabetes does not enable us to distinguish the purely pancreatogenic diabetes due to injury to the islands of Langerhans by inflammation or necrosis of the pancreas from the usual kind of diabetes, where additional extrapancreatic diabetogenic factors are assumed to be at play. It stands to reason that compensatory regeneration of the islands is more likely to succeed in alleviation of the plain hypoinsulinism of the former than of the more complex derangement of metabolism in the latter type of diabetes. Some of the just mentioned cases, with complete remission of the diabetic state and the emergence of hypoglycemic attacks, may well fall into the category of patients described in this paper in whom an overshooting regeneration of the islands of Langerhans converted hypoinsulinism into hyperinsulinism.

Summary

Attention is called to the occasional occurrence of hyperinsulinism in patients with chronic pancreatitis, with obstruction of the pancreatic duct

by concrements or tumor, and with disease of organs adjacent to the pancreas.

The hyperinsulinism encountered in these cases is attributed to hyperplasia and neoformation of the islands of Langerhans following injury to the pancreas.

Review of the literature of the last 25 years reveals that this syndrome has been repeatedly described in the foreign literature but has not been recognized as such in this country.

Summario in Interlingua

Le presente articulo signala le occurrentia sporadic de hyperinsulinismo in patientes con pancreatitis chronic o con cirrhosis e atrophia del pancreas in consequentia de obstruction del ducto pancreatic per concrescentias o tumores o con morbo del vias gastrointestinal o biliari.

Un revista del litteratura del passate 25 annos revela que iste syndrome ha essite repetitemente describite in le litteratura al extero del Statos Unite, specialmente in Francia e Germania, sed que illo ha non ancora essite notate in iste pais.

Le hyperinsulinismo incontrate in tal casos es attribuite al hyperplasia e neoformation del insulas de Langerhans post injurias delivrate al pancreas. Il es possibile que le numero del insulas es reducite, sed certes inter illos o illos omnes es allargate e consiste quasi totalmente de cellulas beta. Le plus grande numero de insulas hyperplastic es a trovar in le portion del pancreas que exhibi le plus extense inflammation e sclerosis. Micre conglomerationes del cellulas insular—quasi omnes cellulas beta—es frequentemente a notar in stato de excrescentia ab le epithelio canalicular. Le preponderantia del cellulas beta causa un displaciamento—frequentemente marcate—del proportion inter cellulas alpha e cellulas beta in favor del cellulas beta que es le productores de insulina. Iste alterationes esseva demonstrate histologicamente in 22 del 43 casos que representa le casuistica del presente articulo.

Le tableau histologic resimila intimemente illo observate in experimentos animal post ligation del ducto pancreatic o resection partial del pancreas.

Inflammation chronic e hyperemia del pancreas, dilatation del ductulos pancreatic, e hyperglycemia es considerate como stimulos possibile del hyperplasia e hyperfunction del insulas.

Specialmente interessante es duo casos de hyperinsulinismo secundari a pancreatitis traumatic, con diagnoses establite per laparotomia exploratori. In ambe iste casos le patiente se presentava con le symptomas e signos de grados marcate de hypoglycemia tres menses post le experientia de un trauma abdominal.

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SYSTEMIC LUPUS ERYTHEMATOSUS AND HYPERTENSION WITHOUT RENAL INSUFFICIENCY *

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In the evaluation of patients with hypertension, specific etiologic factors such as coarctation of the aorta, unilateral renal disease or polycystic disease of the kidneys have been sought, but have been found only occasionally. Continuing improvements in diagnostic methods, however, have made possible the discovery of new factors operative in association with high blood pressure. Among these, we believe that systemic lupus deserves current emphasis.

Since Hargraves' [1] description of the lupus erythematosus cell in 1948 there has been a marked rise in the reported incidence of systemic lupus erythematosus (S.L.E.), due presumably to this new diagnostic aid. A review of the literature indicates that the majority of patients with S.L.E. show marked elevations of blood pressure only in association with severe renal damage. We wish to report the occurrence of S.L.E. in young patients with hypertension who have not reached a stage of renal insufficiency.

Case Reports

Case 1. This young man was examined by Dr. David Platt, of Wilmington, Delaware, in September, 1955, prior to entering college. At this time his blood pressure was 128/85 mm. Hg. In June, 1956, at the age of 18, a tender petechial eruption was noted on the palms of his hands. Shortly thereafter he developed a low grade fever, edema of his face and hands, left axillary adenopathy and 2 plus albuminuria. At this time his blood pressure was 170/120 mm. Hg.

Following consultation with Dr. Leonard P. Lang, the patient was admitted to the Memorial Hospital in Wilmington, Delaware, on July 5, 1956. During this hospitalization his blood pressures were recorded as high as 210/150 mm. Hg. Slight retinal arteriolar narrowing and early arteriovenous crossing defects were described. Fluoroscopic examination and the electrocardiogram suggested left ventricular hypertrophy.

Sedimentation rate (Wintrobe method) was 100 mm. per hour. The blood urea nitrogen ranged from 15 to 20 mg.%. Urinalyses showed albuminuria, with occasional red blood cells and finely granular casts. The phenolsulfonphthalein ex-

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cretion test and intravenous urogram were normal. Three L.E. cell preparations were negative, as were the antifibrinolysin titer, Klein test and a biopsy from the deltoid muscle. His hospital course was marked by progressively severe edema of his left upper extremity, with associated pain in his left arm and leg. He continued to have fever, with daily peaks of 101 or 102° F.

Within twenty-four hours following the use of cortisone, 50 mg. daily, and potassium chloride, 0.5 gm. every six hours, there was striking clinical improvement. The patient became afebrile and his malaise disappeared. The palmar rash, however, recurred at irregular intervals. This remission continued as steroid therapy was gradually withdrawn and was finally discontinued on October 26, 1956. A trial of reserpine, 0.25 mg. twice daily, given for continued hypertension, was followed by mental depression and was accordingly stopped. During the academic year beginning September, 1956, the patient attended college and performed well, being excused from gymnasium and military drills. He complained only of susceptibility to fatigue, and aching of his hands at times when the palmar rash recurred.

The patient was admitted to the Hospital of the University of Pennsylvania for further evaluation on June 24, 1957, there having been a recurrence of fever to 101° F. in the evenings for several weeks, together with arthralgia and evanescent palmar skin lesions. The positive physical findings were as follows: Blood pressures were 200/140 mm. Hg in both arms, 240/150 mm. Hg in both legs. A few red papules were present over the palms of the hands. A large keloid was present over the left deltoid at the site of muscle biopsy. Grade III hypertensive retinopathy was observed, with small cotton-wool exudates and hemorrhages, but only slight arteriolar narrowing. An ophthalmological consultant felt that these findings were consistent with a diffuse collagen disorder. The heart was not enlarged. A soft systolic murmur was heard at the cardiac apex, and the second heart sound was moderately accentuated in the aortic area. The liver and spleen were moderately enlarged.

The blood urea nitrogen was 17 and 19 mg.% on two occasions. Despite continued albuminuria, the phenolsulfonphthalein excretion was satisfactory, with 25% excretion in the first 15 minutes, and 65% in two hours. An intravenous urogram was normal. The serum albumin was 4.4, serum globulin, 2.5 gm.%. An L. E. preparation was not done. A biopsy of an axillary lymph node was interpreted as "chronic lymphadenitis." Smears and cultures of the excised node were negative for tubercle bacilli and pyogens. The serum bilirubin and bromsulfalein dye test were normal. Dr. A. J. Creskoff examined the sternal marrow and reported that slight hyperplasia was evident. A blood count on July 3 was as follows: hemoglobin, 16.1 gm.; leukocytes, 13,000; neutrophils, 82%; monocytes, 10%; lymphocytes, 8%. This was in contrast with a normal leukocyte and differential count on June 26. An intravenous Regitine test was negative for evidence of pheochromocytoma.

Throughout this hospitalization the patient's blood pressures ranged between 180/135 and 205/160 mm. Hg. He was intermittently febrile, with peaks of 101° F. He complained of cramping abdominal pains associated with nausea, vomiting and diarrhea. Periarteritis nodosa was considered to be the most likely diagnosis. He was discharged on July 10, 1957, with the suggestion that he receive steroid therapy.

Because of continuing abdominal pains despite renewal of cortisone therapy, the patient was admitted to the Wilmington General Hospital on July 19, 1957. Gastric suction was instituted two days later because of abdominal distention and was productive of bright red blood. Three days after admission his temperature was 105° F. When circulatory collapse ensued, he improved slightly following the use of oxygen, digitalis and antibiotics. An abdominal x-ray revealed free air under the diaphragm, suggesting rupture of a peptic ulcer. Repeated blood transfusions were given because of a falling hemoglobin. Tarry and bloody stools subsequently were observed. He died suddenly on August 13, 1957.

A necropsy was performed by Dr. J. V. Casella on the day of his death. Dr. Casella described "heart findings of a non-vegetative, verrucous endocarditis of the mitral valve and microscopic findings of widespread fibrinoid necrosis in vessel walls, wire loop changes and fibrinoid thrombi in glomerular capillaries, possible inclusion bodies and increased numbers of plasmacytes in the lymph nodes all of which point to a diagnosis of acute disseminated lupus erythematosus." Additional findings included: (a) a perforating ulcer of the stomach with massive gastrointestinal hemorrhage; (b) abdominal abscesses, multiple; (c) peritoneal adhesions, fibrous, diffuse; (d) segmental gangrene with multiple fistulae of small intestines; (e) hypertrophy of the left ventricle; (f) fatty metamorphosis of the liver; (g) atelectasis, partial, lower lobe of left lung; (h) hydrothorax, left. The immediate cause of death was massive gastrointestinal hemorrhage from a gastric ulcer.

Case 2. A white female was discovered to have hypertension at the age of 18 in 1949. She was treated for four years with a variety of antihypertensive agents, *not including hydralazine.*[2] Because of her failure to respond to this medical regimen, she was referred to us for consideration for surgical treatment of hypertension. She complained of severe frontal and occipital headaches, nausea, vomiting, and marked impairment of vision. As a child she had suffered an episode of rheumatic fever. A kidney infection was treated in 1950, subsequent to the discovery of her hypertension.

At the time of our initial examination in 1953 the patient's blood pressures ranged between 200/140 and 230/170 mm. Hg. There was grade IV hypertensive retinopathy; she was almost blind. A diastolic rumble of mitral stenosis was heard at the cardiac apex by several observers. There were no signs of congestive heart failure. The blood urea nitrogen was 11 mg.%; the phenolsulfonphthalein excretion was 15% in 15 minutes and 50% in two hours. There were slight albuminuria and cylindruria. An intravenous urogram was negative save for slight delay in Diodrast excretion.

In May, 1953, Dr. Harold A. Zintel performed a bilateral subdiaphragmatic sympathectomy and subtotal adrenalectomy in two stages. Although a satisfactory reduction in blood pressure did not result, the patient improved considerably. Her headaches were completely relieved. The funduscopic picture gradually receded to grade II, with disappearance of papilledema, and the resorption of hemorrhages and exudates. She became able to read in comfort. From a pattern of left ventricular hypertrophy, her electrocardiogram reverted to normal.

Adrenal replacement therapy was maintained with cortisone, desoxycorticosterone and supplementary salt tablets. Steroid therapy was maintained at the minimal level consistent with the patient's sense of well-being. She suffered several episodes of mild adrenal insufficiency, with symptoms of generalized weakness and postural hypotension. Adrenal insufficiency was confirmed by hyperkalemia and elevation of the blood urea nitrogen. None of these episodes required hospitalization for correction. Her usual replacement therapy was 37.5 mg. of cortisone, 2 mg. of buccal desoxycorticosterone, and 3 gm. of salt daily. With the addition to this regimen of reserpine, 0.25 mg. twice daily, her blood pressures ranged between 140/100 and 150/120 mm. Hg. Symptomatic improvement continuing, she was married in November, 1954.

Upon her visit to the Adrenalectomy Follow-Up Clinic on December 19, 1956, she complained of malaise, weakness and anorexia, beginning two weeks after dental extractions performed with penicillin prophylaxis. In addition, she noted pain in her left flank and back, together with pain and swelling of the proximal interphalangeal joints of her hands and wrists. She was re-admitted to the Hospital of the University of Pennsylvania with a tentative diagnosis of bacterial endocarditis or a collagen disease. Upon admission her temperature and pulse rate were normal.

The blood pressure was 160/120 mm. Hg. Funduscopic examination disclosed grade II hypertensive and arteriolosclerotic retinopathy. Examination of the heart by several physicians again revealed accentuation of the first sound at the apex, and a mid-diastolic apical rumble with presystolic accentuation. The second heart sound in the pulmonic area was accentuated. A grade II short, blowing apical systolic murmur was also heard. The liver was barely palpable at the right costal margin; the spleen was not felt. There was periarticular thickening of the proximal interphalangeal, metacarpophalangeal, wrist and ankle joints, with fusiform swelling of the proximal interphalangeal joints and limitation of flexion.

Laboratory studies disclosed anemia, with 7.5 gm. of hemoglobin, leukopenia of 3,800, with a normal differential count, and thrombocytopenia of 83,000. The erythrocyte sedimentation rate was 100 mm./hr. Urine specific gravity measurements ranged between 1.015 and 1.020. There was slight to moderate albuminuria. The blood urea nitrogen was 16 mg.%. A reactive Kolmer's test and a weakly reactive Klein test were obtained, both of which had been nonreactive prior to adrenalectomy.[3] *Two L.E. preparations were positive.* Blood cultures revealed no bacterial growth. Subsequently, a fever of 100.4° F. was observed during this hospitalization. With the presumptive diagnosis of S.L.E., the patient was discharged on January 1, 1957, receiving 50 mg. of cortisone daily.

Following discharge, the patient noted gradually increasing dyspnea, cough, occasional orthopnea and generalized edema. She continued to have a low grade fever. She was admitted to St. Francis' Hospital, in Trenton, New Jersey, on January 12, 1957, where she was observed to have a temperature of 102.8° F., a sinus tachycardia of 112, and a respiratory rate of 40. The blood pressure was 180/105 mm. Hg. For the first time a "butterfly" rash was seen on her face. Moist râles were present at both lung bases. The cardiac findings were similar to those noted before. There was edema over the sacrum and ankles. The hemoglobin was 6 gm., blood urea nitrogen, 79 mg.%. *Two L.E. preparations were positive.* She was given digitalis, larger doses of cortisone and transfusions of packed red blood cells. She failed to respond, however, developed convulsive seizures, and died on January 23, 1957.

Necropsy was performed by Dr. Solomon Weintraub. There were small pleural and pericardial effusions, but no evidence of fibrinous exudate was seen on the serosal surfaces. The left ventricular wall was hypertrophied. There was no rheumatic mitral valvulitis. Verrucous vegetations were found on the *atrial* surface of the mitral valve. The ventricular surface of the valve was slightly roughened, but contained no verrucae. These vegetations were felt to be of the type associated with S.L.E., although the lesions described by Libman and Sacks[4] are usually seen on the *ventricular* surface of the leaflets. There was a small, old infarction of the spleen. This organ also showed passive congestion, as did the lung and the liver. Scattered petechial hemorrhages were present in the mucosa of the stomach and colon. The kidneys were small and contracted; their capsules stripped with difficulty. The external surface showed uniformly distributed petechial hemorrhages, giving the appearance of the so-called "flea-bitten" kidney of chronic advanced glomerulosclerosis.

Microscopic study of the kidney revealed marked thickening of the larger arteries, with both hyalinization and necrosis of arterioles. Many glomeruli were hyalinized; others appeared to be essentially normal. There was thickening of the basement membrane of the glomeruli, suggestive of the wire-loop appearance seen in association with S.L.E. Splenic trabecular arterioles showed reduplication of the media, giving an "onion skin" appearance, as described in S.L.E.[5] The mitral valve showed considerable fibrotic thickening, but no fibrinoid necrosis was seen in the heart. (A review of the histologic sections of tissues taken at the time of adrenalectomy revealed several medium sized blood vessels near the right adrenal gland showing

extensive organized fibrinoid degeneration of the vessel wall and endothelial proliferation which almost occluded the lumen.) It was the conclusion of Dr. Weintraub that the findings were compatible with S.L.E. and malignant nephrosclerosis.

Discussion

A review of the literature shows that certain relationships between S.L.E. and hypertension, as demonstrated by the clinical course of our patients, have not been pointed out.[6] In their excellent review of the collagen diseases, Talbott and Ferrandis [7] do not refer to the fact that patients with S.L.E. may develop marked degrees of arterial hypertension relatively early in their course. Soffer and Bader [8] and Haserick [9] report that normal blood pressure and even hypotension is a characteristic finding in patients with lupus. It is our observation that hypertension may occur in S.L.E. occasionally, even before skin manifestations, hepatosplenomegaly or pancytopenia appears. Harvey et al.,[10] in an extensive study of 138 cases of S.L.E., report only 15 of these with blood pressures greater than 140/90 mm. Hg. Of these, eight had azotemia, four had evidence of severe arteriosclerosis, one was recovering from acute glomerulonephritis, and one developed hypertension while receiving cortisone. The remaining patient had only mild hypertension. Tumulty,[11] reporting upon 105 of the same series of patients, in 15 of whom hypertension was present, stated: "In all but one patient, hypertension did not appear until there was a very pronounced degree of renal impairment, including nitrogen retention." In a review of 108 patients with S.L.E. seen at the University of Chile Clinic, Armas-Cruz et al.[12] noted hypertension in only eight. He reported the coexistence of hypertension with marked renal involvement, but called attention to many patients with renal impairment in whom hypertension was absent. Certainly hypertension has rarely been reported as the initial clinical manifestation of S.L.E.

As with many other patients having hypertension, it was not possible to ascertain with certainty whether our patients developed hypertension as a result of nephritis due to lupus which had not yet reached a stage of renal functional impairment, or were suffering from "essential hypertension." Among patients succumbing to S.L.E., "wire-loop" alterations in the glomerular basement membrane have been reported as occurring in a large proportion (up to 70%).[13, 14] Baehr et al.[15] first described these lesions in 1935, but similar histologic changes have been reported since then as occurring in chronic glomerulonephritis, scleroderma, toxemia of pregnancy and the arteriosclerotic kidney of essential hypertension.[16] Our first patient demonstrated renal lesions which the pathologist thought were typical of those seen in S.L.E. In the case of the second patient, however, although wire-loop changes were found in the kidneys, the over-all histologic appearance was more that of advanced chronic arteriolar nephrosclerosis. In this case, however, the diagnosis of S.L.E. was substantiated by additional

findings of positive L.E. preparations twice, verrucous endocarditis, and splenic arteriolar changes. The appearance of S.L.E. late in her course may have been responsible for the terminal picture of uremia. A less attractive hypothesis is that progressive renal impairment from another cause might have excited an exacerbation of latent lupus.

Although it appears unlikely that adrenalectomy per se might have affected the course of S.L.E. in case 2, one cannot exclude the role of steroid therapy, which both patients received. Although it is acknowledged that cortisone and its derivatives may induce a remission in the course of S.L.E., it is questionable that the duration of the disease is thereby prolonged significantly.[17] Reports of the effects of steroids on the renal lesions of lupus appear to be controversial. Dubois et al.[18] included in their study of lupus two patients with severe renal damage who did not respond to large doses of cortisone. Steroid therapy in 13 of Harvey's [10] patients with elevations of the nonprotein nitrogen was followed by return to normal levels in only two. Azotemia actually increased slightly in four, and rose markedly in seven patients after steroid therapy. On the other hand, Mackay,[19] who evaluated the effect of steroid hormones in lupus nephritis by serial renal biopsy studies, reported both clinical and histologic evidence of arrest of the disease in three patients with early lesions. Those patients with severe nephropathies were not improved by the administration of cortisone.

Our first patient responded dramatically to use of steroids at first, but was refractory when they were administered the second time. It is possible that these hormones were influential in altering the final picture of S.L.E. Selye [20] has demonstrated the production of polyarthritis, periarteritis nodosa, nephrosclerosis and cardiac abnormalities in rats receiving prolonged, large doses of desoxycorticosterone acetate.

There have been reports of patients with Addison's disease, treated with adrenal steroids, who subsequently developed polyarthritis and endocarditis.[21, 22] Slocumb et al.[23] presented a series of patients with rheumatoid arthritis who developed signs of hypercortisonism while receiving steroid therapy. Some of these patients presented a clinical picture similar to S.L.E., including the presence of L.E. cells in their plasma. Unlike our patients, their lupus-like abnormalities appeared to be reversible with reduction of steroid dosage.

Libman and Sacks [4] were the first to call attention to changes in the heart associated with S.L.E. Sterile verrucous endocarditis was found post mortem in two of their patients with cutaneous manifestations of S.L.E. Tachycardia and murmurs, usually systolic, are the most common findings pointing to cardiac involvement if one can rule out the effect of anemia, fever and debilitation seen so frequently in S.L.E. More rarely, a diastolic murmur may be heard at the apex as a manifestation of verrucous endocarditis, usually involving the ventricular surface of the mitral valve.

Both of our patients presented apical systolic murmurs which were not

striking in intensity. In case 2, who had a history of rheumatic fever as a child and an apical diastolic rumble, we were surprised to find Libman-Sacks vegetations, instead of rheumatic valvulopathy. Two of Harvey's [10] 138 cases had signs of mitral stenosis, but proved to have verrucous endocarditis at necropsy. Shearn and Pirofsky [24] reported four patients with lupus who had diastolic murmurs, one of which was described as a presystolic rumble.

Libman and Sacks described the following auscultatory findings in one of the four patients in their original paper on atypical verrucous endocarditis: "Just within the apex there was a loud presystolic rumble followed by a snapping first sound. The second pulmonic sound was loudly accentuated." [4] In their patients, vegetations were found on the *ventricular* surface of the mitral valve. Our case 2 had vegetations on the *atrial* surface of the mitral valve, and thickening of the chordae tendineae. In our case 1, vegetations as large as 0.8 by 0.5 cm. were located along the free margins of the mitral valve, leaving the leaflets smooth and glistening. The other valve surfaces showed no abnormalities.

Summary

Two patients with systemic lupus erythematosus presented a clinical picture of severe arterial hypertension without marked impairment of renal function. Both failed to respond to energetic antihypertensive therapy, which in one patient included subtotal adrenalectomy and subdiaphragmatic sympathectomy. The clinical course of these patients suggested a collagen disease. At necropsy, lesions compatible with lupus erythematosus were found in the heart and kidneys. These observations suggested that one should consider the possibility of disseminated lupus, among other etiologic factors, in patients with "essential" hypertension.

Acknowledgments

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Summario in Interlingua

Iste reporto presenta le vista que patientes con systemic lupus erythematose pote exhibir marcate grados de elevation del tension de sanguine sin signos associate de sever dysfunction renal. Il seque que lupus disseminate deberea esser prendite in

consideration como factor possibile in le investigation de causas possibile de hypertension. Iste possibilitate ha non previemente essite signalate. Un revista del litteratura indica que patientes con hypertension e lupus suffre usualmente etiam de azotemia.

Es reportate le casos de duo patientes in qui le morbo comenciava al etate de 18 annos. Ambe iste patientes disveloppava hypertension sin signos initial de dysfunction renal. In le prime caso, illo de un puero, le suspicion esseva que il se tractava de periarteritis. Initialmente ille respondeva ben a cortisona. Un anno plus tarde ille moriva in consequentia de un hemorrhagia massive ab un ulcere gastric. Al necropsia, endocarditis verrucose del valvula mitral esseva constatate, insimul con diffuse alterationes vascular e renal le quales esseva considerate como diagnostic pro lupus.

Le secunde patiente esseva un puera. Illa esseva subjicite a sympathectomia e adrenalectomia bilateral a causa de hypertension. A iste tempore, in 1953, su function renal esseva excellente, e su tension de sanguine se teneva in le region de inter 200/140 e 230/170 mm de Hg. Le facto que su tension sanguinee non respondeva satisfactorimente al operation esseva le causa de un certe apprehension. Tres annos plus tarde, le patiente esseva hospitalisate con malaise, debilitate, e tumescentia del digitos e carpos. Murmures systolic e diastolic esseva audibile al apice del corde. Quatro tests pro cellulas L.E. esseva positive. Le curso del patiente esseva progressivemente adverse in despecto del uso de cortisona. Illa moriva le 23 de januario, 1957. Terminalmente illa disveloppava un si-appellate typo "papilioniforme" de rash in su facie e anemia de progressive grados de severitate. Como le prime del duo patientes in iste reporto, illa exhibiva le lesiones visceral de lupus disseminate.

Iste observationes suggere que on deberea considerar le possibilitate de lupus disseminate inter le altere factores etiologic in patientes con hypertension "essential."

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GOITER AND MYXEDEMA DUE TO IODIDE ADMINISTRATION *

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THE syndrome of goiter and/or myxedema due to administration of iodide preparations has been reported in more than 30 cases since 1945.[1-14] Despite these observations, most of them single case reports, the association of thyroid abnormalities and iodide therapy is not widely recognized.

It is generally accepted that the suppression of function and involution of the thyroid gland of Graves' disease from iodide therapy [15, 16] are peculiar to that disorder and have no counterpart when iodides are administered to a euthyroid subject. The well documented suppression of thyroidal organic binding of iodine induced by large doses of iodide [17, 18, 19] is considered to be a temporary effect. That this is generally true is apparent from experimental work in which suppression of organic binding of iodine disappears after 26 hours, even if iodide administration is continued.[20] The fact that most euthyroid subjects exhibit no thyroid derangement while taking iodides is further evidence that any reduction in hormone synthesis is, in general, a transient phenomenon. However, as indicated by the abovementioned reports, in an occasional patient the effects of iodides are not transient, and goiter or myxedema develops when iodides are administered.

During the last two years we have observed four instances of thyroid abnormalities in subjects receiving potassium iodide for chronic respiratory disorders. These four cases demonstrate that inappropriate and even dangerous measures may be instituted if the iatrogenic nature of the goiter and myxedema is not appreciated. In addition, this unusual reaction to large doses of iodides is of interest in terms of the general effects of these substances on the function of the normal thyroid gland.

CASE REPORTS

Case 1. A 56 year old Caucasian housewife was started on potassium iodide therapy in March, 1956, for an exacerbation of chronic obstructive emphysema. The dose of potassium iodide was approximately 1.5 gm. per day as the saturated solution. Oral bronchodilators were administered concomitantly. After five months of iodide administration a small nodule was noted in the thyroid isthmus; no such nodule had been noted prior to therapy. Shortly after the thyroid nodule was noted the patient complained of increasing lethargy and fatigue. By June, 1957, she presented the typical appearance of myxedema, with puffiness of the face, dryness of the skin, slow speech and mental impairment. The basal metabolic rate was minus 32, and serum

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cholesterol, 320 mg.%. Thyroid extract was begun, its dose being regulated at 60 mg. daily. All clinical evidence of myxedema then disappeared promptly. By October, 1958, the basal metabolic rate had risen to minus 6, and the serum cholesterol had fallen to 270 mg.%. At this point it was decided to discontinue thyroid medication so that the role of potassium iodide in the pathogenesis of her myxedema could be evaluated. No change in the thyroid nodule had occurred while thyroid extract was administered.

After thyroid extract was discontinued the basal metabolic rate fell gradually, reaching minus 22 in 12 weeks. By that time the cholesterol was 390 mg.%, the thyroid clearance was 3.6 and 0 ml./min., the 24-hour thyroid uptake was 0 and 1.4%, and the protein-bound iodine was 36 gamma%. Over this same period, clinical evidence of hypothyroidism again developed, though in milder degree than in June,

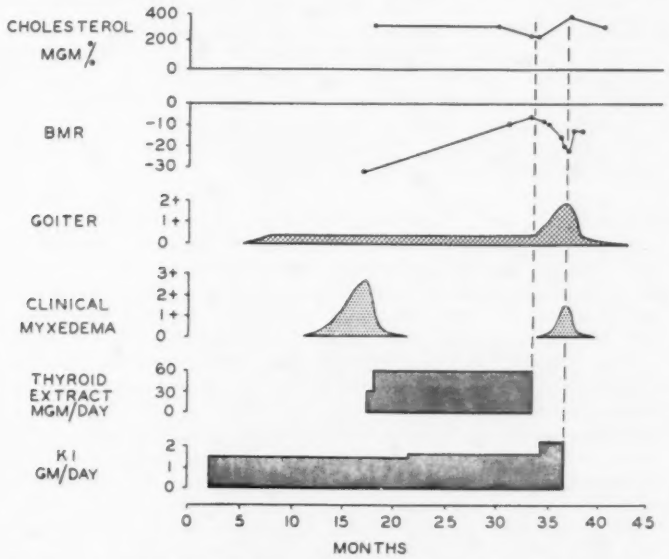


FIG. 1. *Case 1* (G. D.). BMR—basal metabolic rate. KI—Potassium iodide. The degrees of goiter and myxedema represent clinical assessments. Broken vertical lines indicate the times at which thyroid extract and iodides were discontinued.

1957. There was also a dramatic increase in the size of the thyroid gland, which, in addition to a diffuse enlargement, showed a fourfold increase in the size of the previously noted nodule. Potassium iodide, which had been used continuously since March, 1956, was now discontinued.

Within one month of discontinuing iodides, the goiter and myxedema had completely disappeared, the basal metabolic rate had increased to minus 12, and the serum cholesterol had fallen to 275 mg.%.

This patient's course and laboratory findings are depicted in figure 1.

Comment: The true cause of the thyroid nodule and frank myxedema which developed in this patient after 15 months of iodide therapy was not immediately appreciated. Her symptoms were controlled with thyroid ex-

tract, and only after other examples of this iatrogenic thyroid abnormality had been noted in our clinic was the decision reached to attempt to reverse the syndrome by discontinuing iodides. Thyroid extract was first discontinued and the patient allowed to become myxedematous for a second time; while myxedema again developed, there was a marked increase in the palpable goiter. When iodides were discontinued the goiter promptly disappeared, as did all clinical evidence of myxedema. It is apparent that iodide therapy was responsible for the thyroid derangement in this subject, and the thyroid extract controlled the iodide-induced goiter in addition to correcting the signs and symptoms of myxedema. Similar observations have been reported previously.[2, 3, 7]

Case 2. A 52 year old Caucasian male had suffered for many years with a chronic respiratory ailment, eventually diagnosed as "cystic disease of the lungs." By the time potassium iodide was administered, in July, 1956, he was in frank congestive heart failure from cor pulmonale, and required (in addition to iodides) digitalis, frequent antibiotics, and intermittent mercurial diuretics. On the basis of urinary findings and an impaired glucose tolerance, a diagnosis of Kimmelstiel-Wilson disease was also made.

On the program outlined the patient was able to perform sedentary work, but remained dyspneic on very slight exertion. After 12 months of potassium iodide therapy (1.5 gm. per day as a saturated solution), he began to note some rounding of the face. Within the next few months he developed persistent hoarseness, and after 24 months of therapy showed the full picture of myxedema, with dry skin, slow speech and refractory edema. The serum cholesterol followed his clinical course, rising from 245 mg.% in July, 1957, to 300 in November, 1957, and to 360 mg.% by May, 1958. It was not immediately recognized that the myxedema was related to iodide medication, but the patient was advised to discontinue iodides in August, 1958, so that complete thyroid studies might be carried out.

Within three weeks of the patient's discontinuing iodides there was an abrupt deterioration in his cardiopulmonary status. He became dyspneic and cyanotic at rest, and showed frank congestive heart failure, profound weakness, and evidence of respiratory acidosis. Concomitantly, all clinical evidences of myxedema disappeared. One month after he discontinued iodides, the cholesterol had fallen to 130 mg.%. At this time the 24-hour thyroid uptake of I^{131} was 83%. These laboratory findings seemed to confirm the clinical impression that the myxedema had been replaced by a moderate hyperthyroid state. Two weeks later the cholesterol was 85 mg.%. The patient failed to respond to supportive measures in the hospital, and a tracheotomy to facilitate mechanical artificial respiration was performed six weeks after iodides had been discontinued. At the time of tracheotomy the thyroid was noted to be moderately enlarged, soft and extremely vascular, but no biopsy was obtained. The patient died of cardiorespiratory insufficiency one week later. Unfortunately, a postmortem examination was not allowed. The course of this patient is depicted in figure 2.

Comment: In retrospect, it would seem that the myxedema which developed in this patient was helpful in maintaining his precarious cardiorespiratory compensation. Discontinuance of iodides led to a rapid disappearance of myxedema and to an apparent rebound hyperthyroid state. The sudden deterioration of cardiopulmonary status in this patient seems

clearly related to a rapid increase in thyroid activity when iodides were discontinued. A rebound hyperthyroidism after discontinuing iodides has been noted by others,[4, 5, 12] and it is of interest that the case reported by Rubinstein and Oliner [12] died in an episode of "asthma" three months after discontinuing iodides. Another case, reported by VanderLann,[8] developed frank hyperthyroidism two months after discontinuing iodides and was treated with propylthiouracil. This was interpreted as an example of latent hyperthyroidism, rather than as an iodide rebound phenomenon.

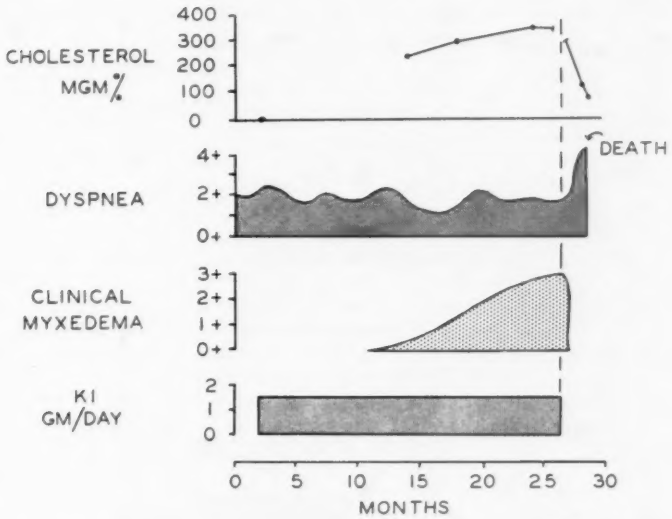


FIG. 2. *Case 2* (J. C.). KI—Potassium iodide. The degrees of dyspnea and myxedema represent clinical assessments. A broken vertical line indicates the point at which iodides were discontinued.

Case 3. A 57 year old Caucasian male was first admitted to the University of Chicago Clinics in January, 1957, with the findings of chronic obstructive emphysema and cor pulmonale. Because of a tendency to prominence of the eyes and some restlessness, the question of hyperthyroidism was raised. This possibility was seemingly excluded by the following tests: basal metabolic rate, minus 8; protein-bound iodine, 4.8 gamma%; serum cholesterol, 200 mg.%; thyroid clearance, 26.4 ml./min.; 24-hour thyroid I^{131} uptake, 50.5%. After the results of these tests had been obtained, the patient was begun on potassium iodide therapy (1.5 gm. per day as a saturated solution) and oral bronchodilators. Prednisone, which had been started previously, was continued.

After six months of iodide therapy the patient noted the gradual development of dryness of the skin. Over the next several months he also noted lethargy and easy fatigue. During the eleventh month of therapy he developed a severe pulmonary infection, and prednisone was discontinued. By the fourteenth month of iodide treatment the patient revealed persistent mild dependent edema and slight rounding

of the face, and over the next five months the picture of myxedema became fullblown, with the addition of hoarseness, slow speech and mental retardation. Chest x-ray showed widening of the upper mediastinum, interpreted as a substernal goiter. By this time the cholesterol had risen to 360 mg.% and the basal metabolic rate had fallen to minus 27. The thyroid clearance and 24-hour uptake were extremely low (0.9 ml./min. and 4.8%, respectively). The protein-bound iodine was 85 gamma%, and the butanol-extractable iodine was recorded as 12.5 gamma%.

Iodides were discontinued. By the end of one month the basal metabolic rate had risen to minus 3 and the cholesterol had fallen to 195 mg.%. All clinical evidence of myxedema disappeared over this same period. Other laboratory studies one

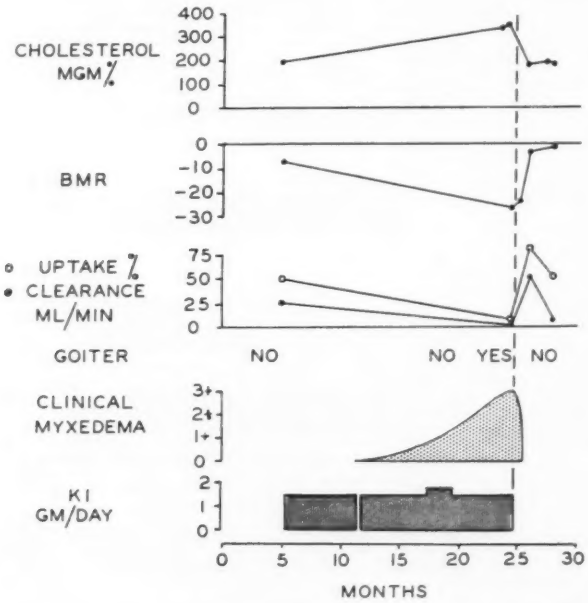


FIG. 3. *Case 3* (J. F.). BMR—basal metabolic rate. Uptake%—24-hour thyroid uptake of I^{131}. Clearance ml./min.—thyroid clearance of serum I^{131}. KI—potassium iodide. The presence of goiter was assessed from the upper mediastinal shadow on chest x-ray. The degree of myxedema is a clinical assessment. A broken vertical line indicates the point at which iodides were discontinued.

month after discontinuing iodides revealed a protein-bound iodine of 11.0 gamma%, a butanol-extractable iodine of 7.9 gamma%, a thyroid clearance of 53.8 ml./min., and a 24-hour thyroid uptake of 85.3%, values consistent with some hyperactivity of the thyroid gland. Repeat chest x-ray revealed a disappearance of the substernal goiter.

Two months later (three months after administration of potassium iodide had been discontinued), the cholesterol and basal metabolic rate were not significantly changed, but the thyroid clearance and 24-hour thyroid uptake had fallen to normal, with values of 6.8 ml./min. and 46.2%, respectively. These findings are shown graphically in figure 3.

Comment: This patient gradually developed myxedema over a year and a half of iodide therapy. Thyroid function was documented as normal prior to iodide administration. When iodides were discontinued there was a prompt disappearance of myxedema and an apparent mild rebound hyperactivity of the thyroid gland. Two months later thyroid studies were entirely normal. While the patient was taking iodides the protein-bound iodine was extremely high. An elevated protein-bound iodine is to be expected under these circumstances, but values as high as 85 gamma% were not encountered by Danowski et al.[21] with equivalent or larger doses of iodide in several normal subjects. In addition, the elevation of the butanol-extractable iodine seen in this patient cannot be explained on the basis of iodide administration alone.[21]

Case 4. A 24 year old Caucasian housewife was first seen at the University of Chicago Clinics in April, 1955, with recurring attacks of bronchial asthma of two years' duration. For a period of one year she had been using bronchodilator medications containing potassium iodide, but these medications had been taken irregularly. After her referral to this clinic the same medication was continued, but was prescribed on a more regular basis. As it was actually used by the patient, this resulted in a daily dose of potassium iodide varying from 125 to 375 mg. daily. After nine months of therapy, a diffuse goiter of moderate size was noted. Basal metabolic rate (done elsewhere) was minus 3. Iodides were continued, and there was no change in the goiter over the following 18 months.

After about three years of iodide therapy the thyroid began to enlarge steadily, and a small nodule was noted for the first time. A repeat basal metabolic rate, done in a private laboratory, was again minus 3. Because of the rapid growth of the thyroid gland and the appearance of an enlarging nodule, a subtotal thyroidectomy was recommended. This was performed at another hospital. Histologic sections revealed flattened epithelium and increased colloid storage (figure 4). Iodides were continued intermittently throughout this entire period.

The patient felt well for one month following thyroidectomy but then began to note puffiness of the face and coldness of the extremities. When seen three months postoperatively she revealed dry skin, pallor, sallow complexion, slow speech, and puffiness of the eyes and face. The basal metabolic rate was minus 15. Iodides were discontinued in order to obtain complete thyroid studies, but with their discontinuance the clinical picture began to improve. Five weeks after the stopping of iodides, all evidences of myxedema had disappeared.

Because of an exacerbation of the patient's asthma, 375 mg. per day of potassium iodide, combined with the use of bronchodilators, were started again in the fall of 1958, and the patient was begun on small doses of prednisone. Within two months she again noted lethargy, fatigue, dry skin, rounding of the face and pallor. These symptoms were not relieved by discontinuing the adrenal steroid, and 11 weeks after resuming iodides the patient appeared to be frankly myxedematous. At this time the basal metabolic rate had fallen to minus 28, and the cholesterol was 610. The thyroid clearance was zero, and the 24-hour thyroid uptake of I^{131} was 0.9%. Iodides were again discontinued.

Clinical evidence of myxedema gradually disappeared during the following month and, at six weeks, the basal metabolic rate was minus 10, cholesterol was 290 mg.%, thyroid clearance, 18.7 ml./min., and the 24-hour thyroid uptake, 45.2%.

The course is summarized in figure 5.



FIG. 4. Section of thyroid gland resected in case 4, revealing increased colloid storage and flattened follicular epithelium (×120).

Comment: It would seem that this patient was subjected to subtotal thyroidectomy because of failure to recognize the iatrogenic nature of her rapidly enlarging colloid goiter. Following thyroidectomy, myxedema developed but was reversible when iodides were discontinued. Sufficient thyroid tissue for normal thyroid function obviously remained. In this patient, the suppressive effect of iodide on the thyroid secretion was not manifest until subtotal thyroidectomy was carried out. A similar case was reported by Bell,[2] and there are recorded examples of myxedema induced by

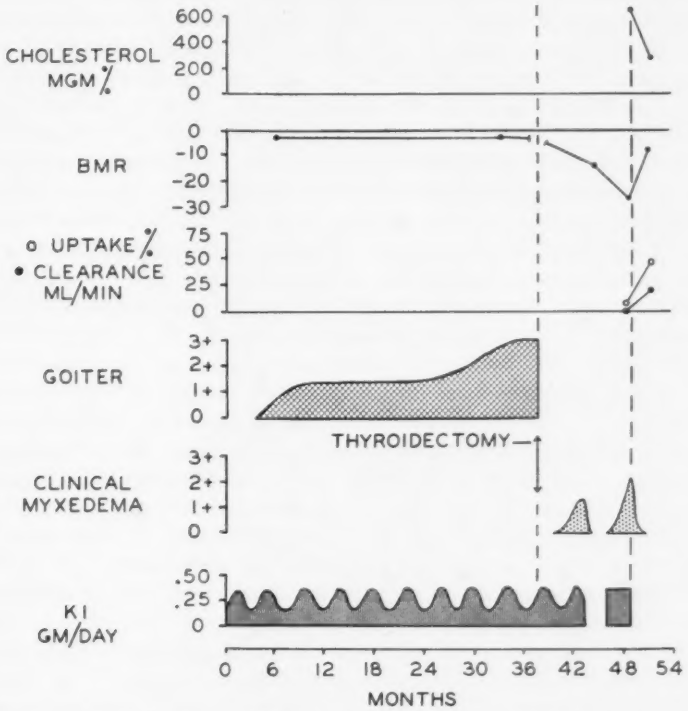


FIG. 5. *Case 4* (R. S.). BMR—basal metabolic rate. Uptake%—24-hour thyroid uptake of I^{131}. Clearance ml./min.—thyroid clearance of serum I^{131}. KI—potassium iodide. The degrees of goiter and myxedema are clinical assessments. Broken vertical lines indicate the times of thyroidectomy and of discontinuing iodides.

iodides in Graves' disease during the post-thyroidectomy period.[11] Previous reports have been in conflict concerning the histologic appearance of iodide-induced goiter (vide infra).

DISCUSSION

It seems firmly established that iodides can produce a clinically significant depression of thyroid function in an occasional euthyroid individual.

Under these circumstances, the excess iodide has been reported to have a physiologic effect similar to that of antithyroid medications, i.e., a tracer dose of I^{131} has been reported to show a relatively high 30-minute thyroid clearance despite a very low 24-hour thyroid uptake.[5] With such findings, the iodide-trapping function of the gland would seem to be unimpaired despite the apparent reduction in thyroidal organic binding of iodine. These results are similar to the acute effects of iodide in the experimental animal.[18] On the other hand, three of the patients in the present report revealed extremely low thyroid clearances while on iodide medication (cases 1, 3 and 5). With the high serum iodide levels undoubtedly present in these cases, I^{131} thyroid clearance cannot be interpreted directly as a measure of iodine trapping, but the clearances as low as 0 to 0.9 ml./min. probably do indicate that the trapping function of the thyroid gland has been exceeded at this iodide level. Similar findings were reported by Childs et al.[22] with large doses of iodide in hyperthyroid subjects, using more detailed methods for studying thyroidal iodine accumulation. These results suggest that thyroidal suppression by iodide is different from that of the thiouracil derivatives, but that there is no difference between iodide suppression in Graves' disease and in the patients reported in the present series.

Relatively few data are available concerning the fractions of serum iodine in patients with iodide-induced myxedema. It is known that, in normal subjects, iodides may produce an elevation of the serum protein-bound iodine, but that the butanol-extractable iodine does not increase.[21] Hydovitz and Rose [10] observed a persistently high nonbutanol-extractable component of the protein-bound iodine in their case, and interpreted this as evidence of an intrinsic defect in thyroid metabolism, this underlying defect having been exaggerated by the administration of iodide. The elevated butanol-extractable iodine in one patient in the present series (case 3) cannot be explained as a normal effect of exogenous iodides. Since thyroid function was documented as normal in this subject prior to iodine administration (including a protein-bound iodine of 4.9 gamma%), it seems unlikely that this patient had an underlying derangement of thyroid function. The possibility that iodides induced the formation of an abnormal organic iodine compound cannot be excluded, but the isolated nature of the observation and the possibility of laboratory error make any definite conclusion unwarranted.

Histologic examination of thyroid tissue obtained at thyroidectomy in one of our cases revealed the typical appearance of a colloid goiter. It is important to emphasize that this patient was taking iodides at the time of thyroidectomy. Similar histologic findings were noted by Bell [2] and by Morgans and Trotter.[4] Increased colloid storage and flattening of follicular epithelium have been noted in experimental animals receiving exogenous iodides,[20] and these phenomena are expected when iodides are administered to the hyperplastic gland of Graves' disease.[16] It would seem

that the histologic effects of iodide are qualitatively similar in Graves' disease and in some euthyroid subjects. However, Turner and Howard [7] reported hyperplasia of the thyroid in one of their patients subjected to thyroidectomy for iodide-induced goiter. This is difficult to explain unless iodides had been inadvertently discontinued prior to thyroidectomy, allowing a compensatory hyperplasia to develop. It is also possible that their patient suffered from some primary thyroid dysfunction, and that the effects of iodide were simply additive. Turner [6] reported an instance of struma lymphomatosa in a patient who had received iodides two years previously and who had a clinical course suggesting that the goiter and myxedema were not causally related to previous iodide administration. It seems important to distinguish cases where there is evidence of preëxisting thyroid disease from those where iodides induce thyroid abnormalities in previously normal individuals, especially since iodides have been implicated by others as precipitating myxedema in certain preëxisting thyroid disorders.[11] The evidence would indicate that iodides induce colloid storage and involution in a previously normal thyroid gland and do not stimulate hyperplasia. These effects are clearly different from those of thiouracil derivatives.

The rapid death of one patient in the present series (case 2) when iodides were discontinued seemed to parallel the development of a rebound hyperthyroid state. Evidence of rebound hyperactivity was also noted in case 3 and in a few previously reported patients.[4, 5, 12] An additional case [8] was considered to have an underlying latent Graves' disease when frank hyperthyroidism developed a few months after discontinuing iodides. In patients with severe cardiorespiratory insufficiency (and such patients often receive protracted courses of iodides), it would seem advisable to be cautious in the discontinuance of iodides in order to prevent or control any rebound hyperactivity of the thyroid gland which may develop. This would seem especially true if myxedema has been induced by iodides; in this instance, the myxedema may be useful in the control of the pulmonary insufficiency state.

A full discussion of the mechanisms of production of thyroid abnormalities by excess iodides is beyond the scope of this paper. On the basis of similarities in the histologic and functional changes induced by iodides in Graves' disease and in some euthyroid individuals, the same mechanisms of action are probably operable in both situations. The dissimilarities with the effects of thiouracil derivatives would seem to indicate that these agents have a different mode of action, and that iodides do not act by directly inhibiting the formation of thyroid hormone. There is evidence that the antithyroid action of excess iodide is enhanced when thyrotropin is present in large amounts,[23, 24] and the theory that colloid storage and hyposecretion are induced by the interaction of thyrotropin and excess iodide is supported by the clinical observation that these phenomena are regularly observed in Graves' disease but only rarely in a euthyroid individual. Also, this theory

would explain the ability of thyroid extract to control iodide-induced goiter; in this instance, thyroid might effect an inhibition of thyrotropin secretion. Skaggs and Cooke [9] report that an iodide-suppressed thyroid is capable of responding to additional thyrotropin, an observation in accord with the experimental observations of Greer and DeGroot.[23] This does not negate the interaction theory, but implies that the effect, if mediated in this way, is dependent upon the relative concentrations of the two interacting substances. Despite these observations, it is apparent that thyrotropin antagonism is not the only mechanism of action of iodide, since organic binding of iodine is inhibited by excess iodide in vitro as well as in vivo.[17] When the various theories are considered, it must be admitted that the mechanisms of action of iodine are not completely understood at the present time. However, it does seem unlikely that iodides act solely to inhibit pituitary thyrotropin secretion, since this would explain neither the in vitro studies nor the observations concerning the protective effect of thyroid extract.

Even more difficult to explain than the suppressive effects of iodide is the apparent variability of response of normal subjects to its prolonged administration. Even if we grant that constancy of dose and length of administration may be important factors, it is still apparent that only a minority of patients develop either goiter or myxedema, even after years of iodide administration. The reasons for this variability of response are completely unknown.

The occurrence of four cases of iodide-induced goiter and myxedema in one clinic over a relatively brief period suggests that this syndrome is not so rare as is generally believed. Patients with idiopathic myxedema should be carefully questioned for a history of previous iodide therapy. With more general awareness of the problem, the authors believe that increasing numbers of cases will be uncovered.

Summary

Four cases of thyroid abnormalities due to potassium iodide administration have been presented. All revealed evidence of myxedema, and three developed clinically discernible goiter. Failure to recognize the iatrogenic nature of the syndrome may lead to inappropriate and even dangerous therapeutic measures. It is believed that iodide-induced thyroid abnormalities are more common than is generally appreciated, and that increasing awareness of the syndrome will lead to recognition of additional cases.

Acknowledgment

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Summario in Interlingua

In despecto de plus que 30 casos de myxedema e/o struma como effecto del administration de iodo reportate in le litteratura, iste syndrome non es extensemente

recognoscite. In le curso del passate duo annos le autores ha observate quatro casos additional in patientes sub tractamento con ioduro de kalium pro chronic disordines respiratori. In tres del casos, allargamento thyroide esseva definitivemente notate.

Un del patientes, un juvene femina asthmatic, esseva subjicite a thyroidectomia subtotal a causa del presentia de un crescente nodulo thyroide. Le examine histologic revelava un struma colloide. Post le operation, myxedema se disveloppava, sed isto esseva promptemente alleviate per le discontinuation del therapia a ioduro. Le altere tres patientes, omnes con chronic emphysema obstructive, disveloppava myxedema post prolongate periodos del uso de ioduro de kalium. In un del casos, le function thyroide habeva essite evalutate ante le initiation del tractamento: Illo esseva completemente normal. In omne le casos, le function thyroide cresceva rapidemente quando le therapia a ioduro esseva interrumpite. In duo del casos, leve formas de stato hyperthyroide pareva manifestar se a iste tempore. Iste apparente effecto de hypercompensation esseva transiente in un del subjectos. In le altere, illo esseva associate con un declino dramatic del stato cardiopulmonar que resultava in su morte. Le myxedema del tertie patiente con emphysema pulmonar esseva tractate con extracto thyroide. Isto resultava in bon regulation del hypothyroidismo sin ulle augmento additional del struma. Tamen, quando le administration de thyroide exogene esseva arrestate, le myxedema recurreva in association con un rapide augmento del dimensiones del glandula thyroide. Omne signos de anormalitate thyroide dispareva quando plus tarde le administration de ioduros esseva discontinuate.

Ben que le mechanismo del phenomeno non es clar, le occurrentia de quatro casos de struma e myxedema inducite per ioduro in un sol clinica e durante un relativemente breve periodo de tempore pare indicar que iste syndrome es minus rar que lo que es generalmente opinate. Non-recognition del natura iatrogene de iste anormalitate thyroide resulta possibilemente in inappropriate e mesmo periculose mesuras therapeutic. Es recommendate que in omne casos de myxedema idiopathic le patiente es questionate detaliatemente con respecto a un possibile historia de therapia a ioduro. Si le hic-discutite association es recognoscite plus generalmente, il es probabile que casos additional va esser reportate.

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CARDIAC INJURY DUE TO NONPENETRATING CHEST TRAUMA *

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The concept of trauma as a cause of heart disease has been well established. Considerable attention has been directed toward the dramatic effects of penetrating chest wounds upon the heart. It should be emphasized that nonpenetrating chest injuries may also produce significant cardiac damage, and that minor amounts of damage occur with great frequency in cases of chest injury.

Our interest in this subject was aroused by following a patient with a myocardial contusion. His electrocardiograms revealed serial changes, but after six months they had not returned to normal. No previous electrocardiogram was available as a base line observation. A search of the literature was made to determine the maximal possible duration of electrocardiographic changes due to cardiac trauma. We were able to find several excellent reviews [1-11] and many case reports with clearly defined pathologic changes, clinical signs and laboratory manifestations. Many authors have expressed the opinion that cardiac injuries occur frequently after this type of chest trauma, and that the majority probably go unrecognized, but no attempts have been made to determine the actual incidence in a series of consecutive cases of chest injury.

The earlier papers stressed the importance of severe permanent changes in the heart due to trauma, while the later ones have more frequently described mild and transient forms of damage. Kahn and Kahn [1] in 1929 felt that even milder injuries of the myocardium usually result in persistent symptoms, signs and disability. The experiments of Bright and Beck [2] showed that the electrocardiographic deviations usually disappeared within a month, and Kissane's study [12] later showed an even shorter duration (only a few to 48 hours). Later case reports have confirmed the observation that the duration of symptoms in such cases may vary greatly, but no summary of the duration of electrocardiographic changes in all cases of cardiac injury has been published.

The purpose of this project, therefore, is to supply more information on the subject, with the main intention of estimating the incidence and the duration of this type of heart disease. In addition, we were interested in determining how serum glutamic-oxalacetic transaminase studies might help in evaluating these cases.

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We have examined unselected patients with various degrees of closed chest injuries. Electrocardiographic studies were used as the primary objective evidence of cardiac trauma. Those patients showing abnormalities were followed as closely as possible until their return to normal.

Method

The patients in this series were admitted to the emergency room of Akron General Hospital after sustaining various types of nonpenetrating chest injuries. No attempt was made to select them according to the severity of trauma. Most patients were seen initially within a few hours after their accidents, all but three within 24 hours. The majority were discharged after a short period of emergency-room observation and followed as out-patients.

At the time of admission in addition to a history and physical examination, each had an electrocardiogram taken. A second electrocardiogram was obtained two days later. (In a few patients, three days elapsed before the second tracing.) Additional cardiograms were done at frequent intervals on those patients showing abnormalities, until they had returned to normal or seemed well stabilized.

Serum glutamic-oxalacetic transaminase levels were determined routinely at the time of the initial two electrocardiograms, and were repeated at frequent intervals in those patients with elevated levels. The normal range in our laboratory is up to 40 units.

The diagnosis of cardiac injury was based on the development of serial electrocardiographic changes following the chest injury, other possible causes of abnormalities being excluded.[13, 14] Those individuals who developed no serial changes and no clinical signs of cardiac trauma within 48 hours were not followed further. Elevated transaminase (SGOT) levels alone were not considered to be diagnostic.

Results

Forty-four patients were followed in this series. Of these, 17 (38%) showed definite evidence of cardiac injury. These are briefly described in table 1.

Onset: As described in the method of conducting this experiment, a time limit of approximately two days was allowed for abnormal manifestations to appear. This was selected because in the majority of documented cases previously reported abnormalities have occurred within 24 hours, and most investigators have agreed that electrocardiographic changes develop within 48 hours. From the review of previous studies it seemed unlikely that manifestations might develop after the first tracing and disappear before the 48-hour interval.

Nine of our patients had serial electrocardiographic changes beginning

TABLE 1

Case	Age	Type of Trauma	Symptoms and Findings	EKG Changes	Duration	SGOT		Other Injuries	Previous Heart Disease
						Day after Injury	Units		
1	18	Thrown from car	Lethargic; subcutaneous emphysema right chest; little pain	T flat 1, $V_{2,6}$ beginning at 2 days	Returning toward normal in 5 days	1 3	40 3	Fracture 1st right rib with 5% pneumothorax	None
2	38	Steering wheel	Tender over right clavicle; bruise anterior right chest	T flat aV_F, inverted $V_{2,3}$ beginning at 2 days	16 days	1 3 6	48 33 34	Fracture of femur	None
3	57	Struck by car	Abrasions of lower chest and upper abdomen; hypotensive first 8 hours due to blood loss. Comatose 18 days	T inverted $V_{2,6}$ beginning at 3 days	15 days	7 9 15	97 67 58	Pelvic fractures Subdural hematoma. Died 17th day	Minimal coronary arteriosclerosis at autopsy
4	34	Automobile accident	Pain and tenderness left lower chest	T inverted 2, 3, aV_F, V_6; beginning 1st day	5 days	1 6	86 21	Fractures left 5th and 6th ribs	None
5	63	Struck on chest by tire-iron	Suprasternal pain radiating to arms for 2 hours	T inverted $V_{4,6}$ beginning 1st day; persistent Q and inverted $T_{2,3}$, aV_F	23 days	1 2 5	25 28 13	None	Angina pectoris
6	19	Steering wheel	Left chest pain and dyspnea; diffuse rales left lung	T inverted $V_{1,3}$ beginning 1st day	23 days	1 3	33 23	5% left pneumothorax	None
7	61	Struck left chest in falling	Pain under left breast	T inverted V_3 beginning at 2 days	4 days	2 4	13 25	None	None
8	34	Steering wheel	Epigastric pain and vomiting; faint systolic murmur at base	T flat aV_F beginning at 2 days	13 days	1 3	39 13	None	None
9	57	Steering wheel	Mild pain in left chest	T inverted $V_{3,4}$, T flat $V_{4,6}$ beginning at 2 days	12 days	3 6	113 42	Laceration of lip	None
10	16	Steering wheel	Pain in left chest; dyspnea	T inverted $V_{2,3}$, flat $V_{4,6}$ beginning 1st day*	30 days	2 3 6 9 15	105 112 58 45 21	Rib fractures; fractures of femur and pelvis; renal contusion	None

* During the first 2 weeks this patient had low voltage in all chest leads and an indefinite transition zone. These changes were caused by a 90% left pneumothorax with shift of mediastinum.

TABLE 1 (*Continued*)

Case	Age	Type of Trauma	Symptoms and Findings	EKG Changes	Duration	SGOT		Other Injuries	Previous Heart Disease
						Day after Injury	Units		
11	24	Steering wheel	Point tenderness 5th rib at right midclavicular line	T wave inverted aV_L beginning on 1st day	2 days	1	8	Nasal fracture	None
12	21	Hit chest against dashboard	Abrasion mid-sternum and 4th left intercostal space	T wave inverted, aV_L, ST elevated $V_{4,5}$ beginning 1st day	T wave 2 days ST 4 days	1 4	21 22	None	None
13	54	Auto accident	None apparent	T flat 1, aV_L, V_{5-6} on 1st day	3 days	1 3	20 20	Fracture 11th rib left	None
14	56	Steering wheel	Sinus tachycardia. None other	ST elevated, 2–3 aV_F. Occasional ventricular premature beat on 1st day	Returning to normal 13 days	1 4 6 8 11	110 50 45 45 57	None	None
15	21	Hit chest on dashboard	None	T wave inversion aV_L and V_1 beginning 1st day	3 days	1 3	13 11	None	None
16	34	Auto accident. Struck face and chest	None	T wave diphasic lead 1, flat V_F, inverted $V_{2,4,5}$, diphasic V_6 beginning day 1	8 days	1 2	21 18	Laceration and contusion of face	None
17	26	Hit chest on steering wheel	None	T wave inverted $V_{1,2,3,4}$, T flat V_{5-6} beginning 3rd day	Return to appearance of 1st tracing 6 days. No further change 3 months			None	No clinical diagnosis; original tracing and 3 months tracing both showed nonspecific changes

at the time of the initial examination, while seven did not develop them until the second tracing. One patient showed changes on the third day but had not had cardiograms taken before this. One other patient, who was not seen until five days after an accident, did not develop any abnormalities in serial studies.

Electrocardiographic Manifestations: The electrocardiographic changes in these 17 patients consisted of transient flattening or inversion of the T waves and, less frequently, ST segment deviation in one or more leads. We found no changes in rhythm or QRS complexes.

Clinical Manifestations: Clinical signs definitely compatible with the diagnosis of cardiac trauma were found in only one patient (case 5), a 63 year old white male who had had angina pectoris with exertion for six weeks prior to his injury. Immediately after being struck on the chest he developed severe substernal pain with radiation to both arms which lasted for two hours. His electrocardiograms showed persistent changes in Leads 2, 3 and aV_F, attributed to the underlying coronary artery disease, and transient changes in $V_{4,5,6}$ attributed to the trauma. In the remaining

TABLE 2

Patients with elevated levels	11
With cardiac injury	6
Without cardiac injury	5
Patients with cardiac injury	17
With elevated SGOT	6
With normal SGOT	11

patients there were no signs or symptoms which would suggest any involvement of the heart by the trauma.

Duration: The duration of the electrocardiographic changes in these patients varied from four to 30 days, with an average of 15 days. Only one patient included here was not followed to complete normality. The tracing in five days had returned to nearly normal, but we were unable to follow him further. Two patients had both permanent and serial electrocardiographic abnormalities. We felt that in one case the permanent changes were due to preëxisting heart disease rather than to injury. The other patient was a 26 year old white female who had no clinical evidence of heart disease and no other explanation for the electrocardiographic changes present in the initial tracing and in a tracing taken three months later. We feel that these are only borderline changes, and probably are a normal variant in her case.

Transaminase Changes:

We found it difficult to correlate transaminase activity with other evidence of cardiac injury. Of the 17 patients with heart injuries, six had elevated levels; however, four of these had other injuries capable of causing this. Five patients had increased levels without electrocardiographic evidence of heart damage.

Severity of Trauma: There was no close association in these patients between the severity of trauma to the chest and the development of cardiac injuries. None of them had extensive crushing injuries. Four of the patients with cardiac injuries had rib fractures, while the other 13 did not; three had fractured ribs and no heart injury.

Pathologic Findings: Only one patient in this series died. Serial electrocardiograms indicated myocardial damage. Death occurred on the seventeenth day from complications of a subdural hematoma. No changes were found in the heart at autopsy. This will be discussed later.

Discussion

Even though the heart is surrounded by the bony thorax, it is less well protected than might be expected. Kahn and Kahn [1] have pointed out that its anatomic position and loose suspension in the thoracic cavity may act as predisposing factors to injury under certain conditions. The natural resiliency of the chest wall may allow considerable compression of the heart between the sternum and the vertebral column. Previous writers have felt that hearts with preëxisting disease are more susceptible to injury.[1, 6, 10, 14]

The awareness of the possibility of such factors and an increasing number of case reports led to several experimental studies within the last 25 years. Bright and Beck [2] in 1935 traumatized surgically exposed dogs' hearts and evaluated the clinical, electrocardiographic and pathologic changes. Moritz and Atkins [15] performed a similar experiment in 1938 and described the pathologic processes at various time intervals. Kissane [12] was able to produce similar changes by striking the intact chests of dogs.

The pathologic findings in this type of injury have been well described from these experimental studies and the results of several autopsies. The basic changes as reported are hemorrhage, edema and fragmentation of muscle fibers.[9, 15] Subpericardial and subendocardial lesions are the most common,[9] but any portion of the heart may be damaged with deeper myocardial contusions, endocardial tears, and pericardial tears, with varying degrees of hemopericardium. The myocardial defects are difficult to distinguish from those of myocardial infarction, and the repair processes are essentially the same. In addition, the coronary arteries can probably be involved either directly or indirectly by compression from adjacent hemorrhage.[3, 16] There has, however, been some controversy over the frequency of this.[8]

The manifestations of these injuries are varied, depending upon the extent and location of pathologic changes and the amount of residual damage. The patients may develop signs and symptoms of any arrhythmia, pericarditis with or without effusion, valvular lesions (due to avulsion), septal defects, ruptures of the heart, heart failure, coronary artery disease and myocardial infarction.[17, 19, 27] Those with milder changes may have no clinical findings.

Traumatic changes may also aggravate the manifestations of previous heart disease.[1, 6]

The most common electrocardiographic changes reported are RST and T wave deviations similar to pericarditis and myocardial disease, with flattening and negativity of the T waves.[9] The abnormalities may be indistinguishable from myocardial infarction. All types of arrhythmias and conduction disturbances have also been produced by trauma.

The functional disturbances do not always reflect the degree of anatomic defect found in the heart. Experimentally, fatal arrhythmias have been produced without demonstrable pathologic changes.[15]

In patients with preëxisting heart disease there is a greater possibility of severe or permanent damage to the already diseased myocardium by chest trauma. Our only case of preëxisting heart disease had only mild and transient electrocardiographic changes, which had been resolved two days before the patient's death. No changes in the myocardium attributable to trauma were noted at autopsy.

The prognosis in these injuries again depends largely upon the degree and localization of damage. There may be no cardiac disability, disability with recovery after varying periods of time, permanent cardiac disease, or death from complications such as cardiac rupture and ventricular tachycardia.

The earlier articles on this subject have depicted cardiac trauma as a relatively rare phenomenon. As larger series of cases were reported it became obvious that a significant number of these injuries must occur. Sigler [5] published a series of 42 cases of severe bodily trauma, not necessarily involving the chest, 76% of whom had demonstrable cardiac damage. Leinoff [14] reported that 50 nonselected autopsies of fatal automobile accidents revealed an incidence of 16%. Fifty-one patients in Lieberman's series [18] were hospitalized after various types of accidents, and evidence of cardiac injury was found in 17%.

This study is designed to compile accurate statistics as to the frequency of cardiac injury in a consecutive series of chest injuries. Our figures at this time indicate an incidence of approximately 38%.

The average duration of electrocardiographic abnormalities was 15 days, with a range of from four to 30 days. We found no permanent electrocardiographic changes which could definitely be attributed to trauma.

The use of SGOT determinations has been a useful adjunct in the diagnosis of myocardial infarction. We had hoped that they might also help in detecting traumatic heart disease. Unfortunately, this has not been the case. Only one third of the patients with cardiac injury as determined by electrocardiographic changes had elevated levels, and, of those, most had other injuries which could have produced the rise. Lieberman et al.,[18] in their study of the effects of bodily trauma on transaminase activity, had similar results, with the exception that all of the patients with cardiac injuries had some increase. They pointed out that injury to any organ with

a high concentration of this enzyme can cause a rise in the serum level. This includes heart, striated muscle, brain, liver and kidney. In addition, patients with long-bone fractures were found to have abnormal concentrations in their series. The presence of other injuries which are often associated with chest trauma makes elevated levels difficult to interpret, and if the cardiac injury does not cause significant necrosis of muscle fibers there will be no rise in the transaminase. These factors subtract from the usefulness of this laboratory test in the evaluation of traumatic myocardial disease.

The low incidence of SGOT elevation in patients showing electrocardiographic evidence of myocardial damage is of interest in that it shows that the muscle damage in the majority of cases is very minor.

The incidence of traumatic cardiac damage caused by nonpenetrating chest injuries has been found to be significant in this series. In all of the cases presented here the damage was mild and transient, although it is recognized that the trauma may be severe.

An important fact, and one that should be reëmphasized, is that a severe degree of chest trauma is not necessary to produce cardiac injury. We feel that, to study chest injuries thoroughly, an electrocardiogram should be included to determine even minor amounts of myocardial damage. Prompt recognition of the presence of cardiac trauma is necessary in order that significant, often fatal manifestations may not be overlooked.

The treatment of cardiac trauma in most cases consists only of the recognition of the entity and the maintenance of careful observation for complications. Due to the type of pathologic changes produced by trauma, anticoagulant therapy is definitely contraindicated. In the rare case, surgical intervention may be necessary if hemopericardium develops. Beck has stressed the possibilities of surgical repair in cases with cardiac ruptures.[2, 17]

Summary

1. Forty-four patients with nonpenetrating chest injuries were observed for evidence of cardiac trauma.

2. Seventeen had definite evidence of injury to the heart.

3. These 17 patients had transient electrocardiographic changes appearing within 48 hours and lasting from four to 30 days.

4. Only one had any clinical manifestations of cardiac trauma.

5. An attempt to correlate transaminase levels with electrocardiographic changes as diagnostic procedures proved fruitless.

6. The pertinent literature was reviewed.

7. The importance of recognition of the frequency of this entity was stressed.

Summario in Interlingua

Quaranta-quatro patientes con non-penetrante trauma thoracic esseva studiate per electrocardiogrammas serial e determinationes de transaminase pro establir le

incidentia e le duration del damno myocardial. Trenta-octo pro cento exhibiva alterationes serial del electrocardiogramma indicative de damno myocardial durante periodos de inter quatro e 30 dies. Le duration medie esseva 15 dies. Le symptomas e signos clinic esseva minimal e esseva usualmente eclipsate per le trauma thoracic. Le nivellos de transaminase non se provava de adjuta in separar trauma thoracic con damno cardiac ab trauma thoracic sin damno cardiac.

Es revistate le litteratura relative a damno cardiac per non-penetrante trauma thoracic.

Es opinate que electrocardiogrammas serial deberea esser includite in le studio diagnostic de vulneration thoracic pro prevenir le eventualitate de ignorar le presentia de damno del myocardio. Ben que in le majoritate del patientes iste damno esseva minimal e transiente, un prompte recognition es necessari a fin que manifestationes significative non pote escappar al attention.

Le tractamento consiste essentialmente de mantener un caute vigilantia con respecto al possibile complicationes. Viste le typo de lesiones pathologic producite per trauma, omne therapia anticoagulante es contraindicate.

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An Address

THE USES OF ELEGANCE*

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ELEGANCE is an attribute which stimulates a variety of responses. Its wide spectrum of meaning renders precise definition somewhat difficult, for its usage has developed far beyond its Latin root, to select. This discussion of elegance assumes that it is a quality which evokes unexpected and attentive admiration and is the result of discriminative selection, a definition embracing the wide range between a tastefully ornate costume, an exceptionally neat scientific experiment and a brilliantly original concept. An exchange student from Greece, writing in *The American Scientist* on "Simplicity and Elegance in Theoretical Physics," defined elegance as "the principle that postulates the adequate representation of a physical problem in mathematical formulae which bestow unity, symmetry and harmony among the elements of the problem."

The Gold-Headed Cane is elegant, as were its carriers, the highly successful London practitioners of the seventeenth and eighteenth centuries. In Macmichael's delightful book on the Cane, elegance of attire may be inferred from the description of Radcliffe's clothes: "His full-bottomed wig was dressed with peculiar care; he had put on his best suit of lilac-coloured velvet with yellow basket buttons, and his air on the whole was very commanding . . . his right hand expanded, and placed upon his breast . . . his left wearing his glove, and resting on his side immediately above the hilt of his sword . . . ." He then "stepped into a gay gilt chariot, drawn by fresh prancing horses," the lackeys looking "with all the insolence of plenty in their countenances." While Macmichael suggests that this display may have been motivated by a love affair, it was too characteristic of what Garrison in his *History of Medicine* calls "the solemn elegance" of this era's physicians for it to be other than a usual manifestation. The art of medicine was so devoid of scientific knowledge that pomp and ceremony were highly useful therapeutic adjuncts.

The prescriptions of the period were remarkable concoctions and, if not elegant, were certainly impressive. Published in 1740, Thomas Fuller's *Pharmacopeia Extemporanea; a Body of Medicines Containing a Thousand Select Prescripts for the Assistance of Young Physicians* is a marvel of imaginative permutations and combinations. His "Water of Millipedes" is as follows: "Take live Millepedes 1 pint and half; fresh Orange and Lemon peel each 3 ounces; white Bread 12 ounces; nutmeg 6 drams; juice of Scabious and Cleaners each 1 pint; whey 3 quarts; make a distillation." Fuller avers that this "de-

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purates the blood, clears the nerves, is useful in distempers of the brain and genus nervosum." It was apparently a real tranquilizer, with dubious side-effects but no addiction potential.

The carriers of the Gold-Headed Cane were artists, not scientists; the works of Newton and Harvey interested them but did not stimulate similar activities. They were, however, patrons of science, and one can find true elegance in the cultural aspects of their lives. Mead, physician to Newton, collected a fine library and was a patron of scholars and artists as well as of scientists. Heberden, a member of the group, though not a carrier of the Cane, is described as an "elegant scholar." Askew was considered to be "a scholar of refined taste, sound knowledge and indefatigable research with everything connected with Grecian and Roman learning." The cultural preoccupations of these eminent Gold-Headed Cane practitioners and their colleagues are as enviable as their lack of personal involvement in science is the reverse. However, I must note that Pitcairn, working in an activist environment, recognized what many modern doctors still fail to appreciate when he said, "The last thing a physician learns, in the course of his experience, is to know when to do nothing but quietly to wait and allow nature and time to have fair play, in checking the progress of disease and gradually restoring the strength and health of the patient."

The last Cane bearer was Matthew Baillie, who died in 1823. His book, *Morbid Anatomy*, published in 1793, was the first systematic text of pathology in English, and its engravings are described as "at once masterpieces of science and elegance." But from our perspective the really elegant feature of this book was the inclusion of case histories correlated with the anatomic abnormalities. This may have been the germ of the clinical-pathologic conference.

When Baillie died the Gold-Headed Cane was deposited in the library of the Royal College of Physicians in London. Macmichael has the Cane complain, "I am afraid there is no chance of my ever emerging from the dark recess I occupy. . . ." But Dr. William J. Kerr freed the spirit of the Cane from the "dark recess," liberating it for the possession of a series of outstanding graduates of your school. Such a spirit is self replenishing; the more given, the more remains.

There was a long gap between Baillie's death in 1823 and the first Cane Ceremony at the University of California School of Medicine in 1939. I shall venture to decrease this gap of 116 years by nominating three men whose lives exhibited such varied and rare elegance that the Cane would have been proud to reside with them. These nominations are made from a broad spectrum of talented contributors to the advance of medicine, a spectrum that extends to the present day. My selections please me, and I hope will interest you, although you may be impatiently thinking of alternate candidates who would be equally deserving of my nomination.

The first was a physician whose orderly and ingenious studies of the dynamics of a disease would be a credit to the most brilliant clinical investigator of our day. W. B. O'Shaughnessy was born in Limerick in 1809. His life overlapped that of Matthew Baillie, and he was 14 years old when the Cane was retired. He received his M.D. at Edinburgh in 1829 and came to London to practice thereafter. He found to his disappointment that London medicine was a closed corporation; no one could practice without permission of the London

College of Physicians, which had been granted full legal control by Henry VIII and still had power to imprison anyone unlicensed by the College who practiced within seven miles of London. We hear O'Shaughnessy, aged 22, saying bitterly at a meeting of practitioners at the Crown and Anchor on May 4, 1831, "I am a graduate of the University of Edinburgh. Circumstances induced me to move from that capital to London, and the moment I arrive here I find myself totally unable to practice my profession." Yet the restrictions of the Royal College of Physicians were the first attempt in England to regulate the quality of medical practice.

Cholera had been pandemic for some years when O'Shaughnessy arrived in London. *The Lancet* of that day was so replete with notes and letters about cholera that one J. C. Badeley, of Chelmsford, sent in a Latin poem to *The Lancet* entitled "In Scriblomania de Cholera." The treatments advocated were almost all ingenuously contrived to augment the processes that were destroying the patient: calomel and castor oil for the diarrhea; bleeding, although there was frequent comment on the impossibility of obtaining blood from the collapsed veins; emetics; and rectal instillation of "mutton tea, viz., a strong infusion of lean good mutton *avoiding* salt and spices."

Even O'Shaughnessy presented a paper to the Westminster Medical Society on December 3, 1831, recommending the intravenous injection of potassium chlorate, reasoning that the oxygen unsaturation so obvious in the patient with "blue cholera" could be remedied by this toxic oxidizing agent. Elaborate and well written, it was essentially armchair thinking, backed up by two rather irrelevant experiments on asphyxiated dogs. He apparently did not pursue this thesis.

I wish we could trace his steps between this speech on December 3 and the letter he wrote to *The Lancet* on December 29. He had expressed in the speech some doubts as to his chemical data, which he had derived from Germany; this may have moved him to an investigation of his own. In any event, he went to Newcastle upon Tyne and carried out an elegant study of the pathologic physiology of cholera that will always be a model of brilliant chemical research. In an era of empiricism and, at its best, only descriptive classification, he was concerned with the quantitative dynamics of a disease, applied the experimental method, and reached a solution unchallenged to the present moment. The elegance of O'Shaughnessy's mind can best be demonstrated by quoting his brief but thoroughly inclusive letter to *The Lancet* describing his results:

"Sir, having been enabled to complete the experimental inquiries on which I have some time back been engaged in Newcastle-upon-Tyne I beg you will have the kindness to give insertion to the annexed outline of the results I have obtained:

"1. The blood drawn in the worst cases of the cholera is unchanged in its anatomical or globular structure.

"2. *It has lost a large proportion of its water,* 1000 parts of cholera serum having but the average of 860 *parts of water.*

"3. It has lost also a great proportion of its neutral saline ingredients.

"4. Of the free alkali contained in healthy serum, not a particle is present in some cholera cases and barely a trace in others.

"5. Urea exists in the cases where suppression of urine has been a marked symptom.

"6. All the salts deficient in the blood, especially the carbonate of soda, are present in large quantities in the peculiar white dejected matters."

Thus, he proved that the copious diarrhea of cholera, as it sweeps out water and salt, causes dehydration, electrolyte depletion, acidosis and nitrogen retention. This elegant quantitative analysis of fluid and electrolyte physiology well deserves our Gold-Headed Cane.

Some weeks later a more nearly complete report included a pioneer step in therapy, viz., basing therapy on the physiologic demands clearly evident from an understanding of the mechanism of a disease, rather than on old wives' tales or on empiric pronouncements. The biochemical disturbances which he had demonstrated suggested to O'Shaughnessy that the treatment must depend on two principles: "First, to restore the blood to its natural water content; secondly, to restore its deficient saline matters." This could be accomplished, he stated, by the "injection into the veins of tepid water holding a solute of the normal salts of the blood." It is a sad example of the tenacious hold of tradition that this conclusive contribution to the treatment of cholera reached no routine use until it was employed by Rogers in India in 1906, where it resulted in a significant reduction of the mortality rate.

About a year and a half after his investigation of cholera, O'Shaughnessy went to India with the East India Company. He continued to write in the ensuing years, but none of it was comparable in brilliance or originality with the work on cholera. Indeed, his chief interest soon focused on the newly invented telegraph, and as Director General of Telegraphs for India, he created a 4,000-mile network that was credited with saving India for the British during the famous Mutiny. He was knighted in 1856, and changed his name to Brook in 1861. I hope that a proper biography of this extraordinary man will be published some day.

Since the spirit of the Cane has already been brought to America by Dr. Kerr, I have no hesitation in crossing the Atlantic to find my second interim candidate. This man rivaled the original cane-bearers in his scholarly appreciation of the classics, and almost equalled O'Shaughnessy in his scientific contribution to the advance of medicine. Oliver Wendell Holmes was born in 1809, the same year as O'Shaughnessy. Delayed somewhat by an unhappy year at law school, which he described as "very cold and cheerless," he entered Harvard Medical School just about as O'Shaughnessy was being graduated from Edinburgh.

There is hardly a facet of this talented man that does not evoke unexpected and attentive admiration. He was a poet:

> "Build thee more stately mansions, O my soul,
> As the swift seasons roll!
> Leave thy low-vaulted past!
> Let each new temple, nobler than the last,
> Shut thee from heaven with a dome more vast,
> Till thou at length art free,
> Leaving thine outgrown shell by life's unresting sea!"

His novel, *Elsie Venner,* is recognized as showing an "understanding of psychology well ahead of his time." I have just reread this novel, and find his

perceptive and intuitive interpretation of human behavior much more acceptable than the ostentatiously Freudian-guided stories of recent decades.

Holmes was a wit and a satirist; in the brilliant circles of the Boston literati, he was their most erudite conversationalist. *The Atlantic Monthly* was named by him, and its early survival was due to the popularity of his "Breakfast Table" series. Nor should it be omitted that he fathered the greatest jurist of our times.

Holmes's literary fame has somewhat overshadowed his medical reputation. Yet had he never published a verse, his medical writings alone would have kept his name alive. Before presenting his most famous scientific contribution, I would like to recall some of his comments on medical education and the philosophy of medicine in general.

Holmes was Professor of Anatomy at Harvard Medical School for many years, and was Dean for part of that time. It is often recounted that his lectures on anatomy were so witty and entertaining that he was regularly scheduled for that fatigue-ridden portion of the day when the average lecturer merely soothes the audience to sleep. His belief that it was not necessary to learn every contour of a bone required, sadly, many decades for acceptance.

Were I not certain of discovery, I would be tempted to read on this occasion Holmes's Valedictory Address delivered to the graduating class of Bellevue Hospital College in 1871. It was entitled "The Young Practitioner," and was crammed with wise and gentle advice expressed in the happiest literary style. Justifying the time used in the teaching of less immediately practical facts, he says, "The knowledge of today finds soil in the forgotten facts of yesterday. You can not see anything in the new season, of the guano you placed last year about the roots of your climbing plants, but it is blushing and breathing fragrance in your trellised roses; it has scaled your porch in the bee-haunted honeysuckle; it has found its way where the ivy is green; it is gone where the woodbine expands its luxuriant foliage." What a charming way to say, "Don't regret your anatomy and chemistry." But, inconsistently, he urges, "Do not linger by the enchanted streams of literature." He faces the age-old ethical questions of truth by saying bluntly, "Your patient has no more right to all the truth you know than he has to all the medicine in your saddlebag. I have seen a physician examining a patient's chest stop all at once, as he brought out a particular sound with a tap on the collar-bone, in the attitude of a pointer who has just come on the scent or sight of a woodcock." Our modern equivalent is the doctor who whistles in alarmed surprise at the height of a blood pressure reading.

At a time when medical curricula contained little but lectures, Holmes approved of teaching "real and most valuable knowledge by making the student work, and work thoroughly, in the laboratory" (1883), and on another occasion he said, "The bedside is always the true center of medical teaching."

It is fascinating to observe, as one reads Holmes's essays on medical subjects, that he is preoccupied on many occasions with the supercilious attitude of the "practical" men toward the scientific aspects of medicine. His statement 75 years ago has a familiar note: "The self-styled practical men of provincial celebrity sometimes sneer at the labors of the pathologist, as ignorant sailors laugh at the land-lubber who computes their captain's logarithms; alike un-

conscious that their path through doubt and danger is traced by the hand which is the object of their stupid laughter." He compares the unscientific practitioner to the Arctic explorer who, while slogging along toward the North Pole at 10 miles a day, found that the ice flow under his feet was moving in the opposite direction at the rate of 12 miles, an elegant analogy. We are still in the throes of the old struggle between those who would divide the art from the science of medicine, thus degrading the physician to the level of an artisan, plodding backward on the ice floes of ignorance. I wish the elegance of Dr. Holmes's prose were available today to be directed against the anti-intellectualism of some of our medical leaders.

When my nominee for the Gold-Headed Cane wrote, "The art of healing is supported, advanced and illuminated by the various kinds of knowledge which are recognized as belonging to the science of medicine," he was in no sense speaking as a mere theorist. In that era of bleeding, blisters and fatuous prescriptions, he declares, reminding us of Pitcairn, "I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be better for all mankind, and all the worse for the fishes." And in another essay: "The disgrace of medicine has been that colossal system of self deception, in obedience to which mines have been emptied of their cankering materials, the vegetable kingdom robbed of all its noxious growths; the poison bags of reptiles drained of their venom and all the inconceivable abominations thus obtained thrust down the throats of human beings. . . ." Moreover, he brilliantly points out that, with less medication, more attention might be given to the management of the patient himself, even anticipating the wise aphorism of Francis Peabody when he says, "To *cure* a patient is simply to *care* for him," the most elegant of all ideals for the guidance of the healer.

In 1843, aged 34, Holmes presented to the medical world his paper on "The Contagiousness of Puerperal Fever." There had been intimation for some years that this disease was spread by contagion, but Holmes's scholarly essay was the first collection of unassailable scientific proofs. While it stimulated much quiet approval, the dissent was noisy, vituperative and thoroughly illogical. The worst offender was a famous Philadelphia obstetrician, Charles Meigs, Professor of Obstetrics at Jefferson Medical School, a man 17 years older than Holmes. This man was still voicing his bitter and illogical disbelief 10 years later.

Not only did Holmes gather together a mass of clinical material from his own experience and that of his friends, but he also culled from the literature innumerable case records supporting his thesis. Furthermore, he drew up a set of rules for midwives and obstetricians that could have been little improved had he been aware of the existence of streptococcal infection. This elegant manifestation of scientific logic and investigative energy saved innumerable young mothers from early death. And so Holmes enters the Hall of Fame in science as well as in literature.

Before presenting my final Cane selection I would beg your indulgence for the description of a curious misuse of elegance to which I was exposed as a medical student. I arrived at the Johns Hopkins Medical School in 1911, during the heyday of physical diagnosis. At a time when biochemistry was discussing the structure of nucleic acid, clinical medicine was presenting physical

diagnosis as an independent discipline which had made little sophisticated progress in the many years since Auenbrugger and Laennec. Physical signs were collected with less interest in their relevancy than in the virtuosity by which they were obtained. Elegance was the keynote of percussion; in vain did I try to develop the graceful wrist action that would have been more appropriate to Paderewski's piano playing. It was not sporting to look at a chest x-ray until the patient had been worn out by a tiresome period of physical diagnosis, and much time was spent on estimating the blood pressure by palpation before the sphygmomanometer was applied, although the inaccuracy of palpation had long since been proved. As I look back, I realize that it was a misuse of elegance to draw a clef and place the heart murmurs on it in absolute pitch. Holmes, in 1844, observed that "the errors of stethoscopists spring much oftener from faults of their brains than of their ears." Physical diagnosis went through a painful adolescence before it became the useful but less important technic of today. But I envied the elegance of my instructors, and suffered from my inability to emulate it.

Into this atmosphere of preoccupation with clinical minutiae, there came in 1914 my final nominee for the interval Cane. I am proposing him because he was one of the first modern internists to think in terms of the natural history of a disease and its dynamics, and because he had the courage and vision to be the first full-time professor of medicine in this country. Theodore Janeway came to the Johns Hopkins from the professorship of medicine at Columbia and from a lucrative practice in New York City.

Graham Lusk, in the memorial he wrote for the *American Journal of the Medical Sciences* (February, 1918), following Janeway's death, states that he was the first instructor in medicine in New York City who attempted to teach his subject from "the standpoint of disease being a deviation from the physiological normal," and observed further that he was the first man to take routine blood pressures in his office, having designed a portable apparatus for that purpose. Janeway's book, published in 1904 and titled *The Clinical Study of Blood Pressure,* is a classic, and his analysis of the various routes that are followed in the evolution of hypertension was an original contribution to the understanding of hypertensive disease, unexcelled to this time. It was my rare privilege to be a fourth-year student when Dr. Janeway came to the Johns Hopkins, and to work closely with him later as an intern. I have never had a more memorable experience than the discovery at his hands that there was more to the examination of a patient than the goal of an accurate antemortem autopsy, that in clinical medicine the dynamics of a disease is as exciting as its pathologic anatomy.

In 1912, at a period when the clinician was hypnotized by physical signs, and diagnosis was largely reminiscent ("This woman reminds me of a case I saw in consultation three years ago, she was the wife of a prominent banker," etc.), Janeway wrote that medicine is "now consciously an experimental science," and he spoke accusingly of the "intensely practical men" who "discourage all attempts at systematic thinking, who decry laboratory studies and hold that a true knowledge of disease can be acquired only at the bedside." To quote further from the same essay: "When we have comprehended a disease . . . we see it not as an entity, not static, but as something dynamic, a process. . . . All

treatment of disease is a therapeutic experiment, based on a theory. This theory we call a diagnosis. . . . The science of disease (is) the only sure basis for the successful practice of the art of medicine." I can testify from sad memory that this precociously enlightened attitude toward clinical medicine was considered by most of my associates as little short of heresy, and silly heresy at that.

Valuable as were Janeway's scientific contributions and his advanced medical philosophy, his early recognition of the importance of academic full-time in the clinical departments outshines his other achievements. His dedicated unselfishness led him to put his beliefs to the test of action at great personal sacrifice. Leaving lifelong friends and associations, accepting a large cut in income, he went to Baltimore to aid the Johns Hopkins in the final phase of its great experiment in medical education, the introduction of true university standards; for this I award the Cane. The basic sciences had long since been on a university basis, but the clinical departments were in the hands of unsalaried practitioners, obviously not able to give full attention to their university chairs.

In 1912 Janeway had said, in a lecture at Harvard, "Freedom from the need to practice must be secured by the provision of liberal salaries for the men who are to make academic careers in clinical medicine," and he stated further, "In a university, research is the most important means for the education of teachers themselves."

Introduction of the academic full-time policy, with its corollary that research laboratories should be an integral part of the clinical equipment, was the turning point of medical education in this country and thus of medicine itself. The 45 years since Janeway went to the Johns Hopkins have seen a greater advance in the understanding and management of disease than had the previous 500 years. Much of the new knowledge, and most of its critical application to patient care, are the result of freeing the clinical teacher from the distractions of private practice and offering him both the time and the facilities for his own research. With investigative experience the academic physician became a better teacher, a sounder critic of new scientific contributions and a more competent clinician, for modern medicine depends more on a logical thinking than on encyclopedic knowledge. The ivory tower is a lighthouse for the clinical navigator as well as a protected retreat for thoughtful scientists.

I have no more Canes to award, but I would commend to your attention a final elegance—the elegance of that fusion of the healer and the scientist which constitutes the true art of medicine. This fusion is best expressed in the virtuosity required for the integration of all of the components of a diagnostic study into the total appraisal of a single individual, his biologic portrait. This process involves an understanding of that single individual, both by psychology and by intuition, a compassionate response to his anxieties, comprehension of his environment, and a critical evaluation of the highly technical data illuminating the organic status. The final essential requirement is wisdom in the synthesis of these varied components into a basis for life management. Like all great art, the art of medicine is the skillful and creative application of a scientific discipline to a human problem. As Ruskin wrote, "Fine art is that in which the hand, the head and the heart of man go together."

It is my, perhaps prejudiced, conviction that Medicine is the only profession that gives unlimited opportunities for combining the richness and the joys of both the scholar and the humanist. And it offers the broadest spectrum of potential relationships between man's accumulated knowledge and his heart. To the winner of the Gold-Headed Cane and to all this year's graduates I give my sincerest congratulations on your choice of the most elegant of all professions, and I hope that you will wear your M.D. with the realization that the physician can offer an inner elegance of mind and heart that carries as much distinction and is as enduring as the precious metal in your Gold-Headed Cane.

CASE REPORTS

ASSOCIATION OF MYASTHENIA GRAVIS AND HYPERTHYROIDISM, SHOWING RECIPROCAL RELATIONSHIP: REPORT OF A CASE AND REVIEW OF THE LITERATURE *

By Jacob John Robbins, Captain (MC) USN, and Joseph S. Burkle, Captain (MC) USN, *St. Albans, N. Y.*

Myasthenia, or muscle weakness, is not an uncommon symptom in toxic goiter, but the coexistence of myasthenia gravis and hyperthyroidism has rarely been reported. MacLean and Wilson,[1] adding one of their own, tabulate 11 cases previously reported. In view of the long duration of life in myasthenia gravis, and the frequency of hyperthyroidism, the concurrent appearance of the two conditions, on the basis of statistical probabilities alone, could be expected to be much higher than the literature suggests. However, Kane[2] states that, when patients with chronic thyrotoxic myopathy and exophthalmic ophthalmoplegia are eliminated, there are fewer than two dozen well documented cases.

Of considerable interest, both for providing a clue to the pathophysiologic mechanism involved in the two diseases, and as a guide to therapy, is the effect of thyrotoxicity and antithyroid therapy on the state of preëxistent myasthenia. Observations on this point vary considerably in the cases reported in the literature. Thorner in 1939[3] first called attention to a "see-saw" relationship between the two conditions, wherein occurrence of hyperthyroidism appeared to ameliorate the myasthenia, and radiotherapy of the thyroid gland made the myasthenia worse. Bauer[4] and others have reported the rapid deterioration and death of patients in myasthenic crisis following treatment of intercurrent hyperthyroidism. On the other hand, Thorn[5] observed no significant change in the state of the myasthenia following response to antithyroid therapy. Bartel[6] reported some improvement in one of his patients following partial thyroidectomy, but death in myasthenic crisis occurred following total resection. Two of his patients improved after surgery, but the effect of thyroidectomy is difficult to evaluate, since thymectomy was performed at the same time. MacLean and Wilson consider a reciprocal "relationship" as always present, and surgical intervention as dangerous.

It is the purpose of this communication to add to the well documented cases in the literature the following observations on a young woman who developed

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hyperthyroidism while under treatment for myasthenia, and to record the effects on the myasthenia gravis when she was treated with propylthiouracil.

Case Report

This 26 year old white female was first seen in 1957 during a prenatal examination in consultation for control of myasthenia gravis.

In 1953 the diagnosis of myasthenia gravis had been made at another institution and thymectomy performed. Since that time the patient had been maintained on from 10 to 14 tablets (15 mg.) of neostigmine per day. Whenever medication was withheld she experienced extreme fatigue and weakness, and slurring of speech and ptosis were noted. At the time of her first visit, and on subsequent examinations during the remainder of her prenatal period, the myasthenia gravis was under excellent control, and no change in therapy was considered to be necessary. Two months following full term delivery of her normal child she was referred by the obstetrical department because of a 30-pound weight loss and nervousness manifested by irritability and nightmares.

Physical examination at this time revealed a striking change in the patient's appearance. Whereas during previous examinations she had been a somewhat obese, placid young woman, she now showed evidence of weight loss, and was extremely agitated and apprehensive. Pulse rate was 104/minute; blood pressure, 120/60 mm. of Hg. Her eyes were prominent, but no true exophthalmos was observed. There was a fine tremor of the outstretched hands and of the protruded tongue. The thyroid gland was enlarged to three times normal size, and was smooth and firm. The scar of the thymectomy was well healed. Multiple small, nontender cystic masses were palpated in both breasts. There was a grade III harsh systolic murmur over the pulmonic area. Neostigmine requirements were from six to eight tablets daily. Laboratory studies on January 19, 1958, showed a basal metabolic rate of plus 39%, an initial 24-hour I^{131} uptake of 74% by the thyroid gland, a protein-bound I^{131} conversion ratio of 97%, and a 24-hour saliva protein-bound iodine I^{131} ratio of 14 to 1. After receiving tri-iodothyronine, 100 μg./day in divided doses for eight days (suppression test), the patient's studies were as follows: 24-hour I^{131} uptake, 82%; conversion ratio, 100%; saliva protein-bound iodine ratio, 2 to 1.

Clinical Course: On initial therapy of 300 mg. propylthiouracil in three divided doses the patient slowly gained weight, and her tremor and anxiety subsided. The thyroid gland at first enlarged and then gradually became smaller. On April 1, 1958, her 24-hour I^{131} uptake was 52%, and her 24-hour protein-bound I^{131} conversion ratio was 60%.

The patient's neostigmine requirements rose to 10–14 tablets per day, and by June, 1958, she had gained 15 pounds. Propylthiouracil was reduced to 150 mg., and was discontinued in August, 1958. The patient remained well until November, 1958, when weight loss and further anxiety and tremor returned. Her thyroid gland had again increased in size, and the 24-hour I^{131} uptake was 65%. At this time her requirements of neostigmine were eight tablets per day. Antithyroid medication was again administered. In March, 1959, her weight returned to normal (150 pounds), pulse rate was 80/minute, and no tremor of the outstretched hands was noted. Her neostigmine requirement was 12–14 tablets per day. She was taking propylthiouracil, 50 mg. every eight hours.

Comment

The diagnosis of myasthenia gravis had been well established in this patient at an outstanding medical center three years prior to her development

of hyperthyroidism. At that time, as well as when seen by us during repeated prenatal examinations, no evidence of thyroid dysfunction was noted. Following thymectomy, myasthenic symptoms were well controlled with from 10 to 14 tablets of neostigmine daily. Findings two months post partum were unequivocally those of hyperthyroidism as to symptomatology, clinical findings and laboratory studies. In view of the experience of MacLean and others, it was felt advisable to employ a reversible form of antithyroid therapy. Response of the thyrotoxic state was satisfactory, although a daily maintenance dose of 150 mg. propylthiouracil has been found necessary to date. Close observation during periods of euthyroidism and recurrent thyrotoxicosis when antithyroid medication was temporarily discontinued has tended to support the impression, referred to by a number of observers, of the existence of a "see-saw" relationship between the two diseases.

Up to the present time there has been no difficulty in controlling the myasthenic symptoms while the patient was on a maintenance dose of propylthiouracil.

Discussion

In view of the frequent occurrence of myopathy in thyrotoxicosis, proof of the coexistence of myasthenia gravis frequently presents a difficult problem in diagnosis. Where myasthenia occurs first, and the patient has been under observation for a number of years (as was our patient before emergence of thyrotoxicosis), resolution of the problem is not too difficult. However, in the circumstance where thyrotoxicosis predates or is found to be coexistent with myasthenic symptoms, clear-cut delineation of the two diseases is not so easily made. Many workers accept improvement following administration of neostigmine, and aggravation by curare, as criteria diagnostic of myasthenia gravis, but a similar if not so pronounced effect has been reported in thyrotoxic myopathy. Millikan [7] states that marked weakness of other than ocular muscles, and then only in the presence of exophthalmos, is practically nonexistent in myasthenia gravis. Laurent [8] and Brain [9] are firmly of the opinion that thyrotoxic myopathy can be cured by thyroidectomy, but thyroidectomy without thymectomy has never cured myasthenia gravis.

That the neuropathologic defect in myasthenia differs from that found in the myopathy of hyperthyroidism appears to be clear from both clinical and pharmacologic evidence. The defect in myasthenia gravis is considered to be either deficient production or excessive destruction of acetylcholine at the myoneural nerve junction. By protecting acetylcholine, neostigmine, an anticholinesterase, relieves the symptoms of muscle weakness and easy fatigability. What role, if any, thyroxine plays in this mechanism appears highly problematic, particularly in view of the frequent paradoxic improvement of myasthenia in the presence of hyperthyroidism. Moreover, no significant alteration of thyroid function or thyroxine blood levels has ever been demonstrated in uncomplicated myasthenia.

Summary

1. The twenty-third instance of the coexistence of hyperthyroidism and myasthenia gravis is reported.

2. A definite "see-saw" relationship between the two conditions was noted,

wherein appearance of the thyrotoxic state ameliorated the symptoms of myasthenia, and antithyroid therapy increased the neostigmine requirement.

3. Review of the literature indicates that this effect is by far the more common occurrence, although adequate therapy of the thyrotoxic state can usually be accomplished.

4. In view of this and of the many other reported instances where radical antithyroid therapy has been followed by marked aggravation of myasthenia and death in myasthenic crisis, a reversible form of therapy, such as antithyroid drugs, rather than I^{131} or surgery, appears to be the preferable treatment for hyperthyroidism.

Summario in Interlingua

Debilitate muscular es frequente in thyrotoxicosis. Le occurrentia de hyperthyroidismo in un patiente con pre-existente myasthenia grave rende probabile un aggravation del myasthenia, durante que le tractamento del hyperthyroidismo rende probabile le melioration de illo. Ben que iste relation non es un nove discoperta, le reportos in le litteratura nota le plus frequentemente un alternation del effectos de reciprocitate. Un numero de casos se trova in le litteratura in que le tractamento de hyperthyroidismo esseva sequite per morte in un crise myasthenic.

Un patiente feminin de 26 annos de etate con previemente establite myasthenia grave qui disveloppava hyperthyroidismo esseva tractate con doses moderate de propylthiouracil. Esseva notate un relation leve sed definitemente reciproc, evidentiate per le augmento del requirimento del parte del patiente de prostigmina quando le thyrotoxicosis esseva ben regulate e per le melioration del myasthenia quando le thyrotoxicosis recurreva.

Es proponite, per consequente, que un forma reversibile de therapia, del typo hic describite, es indicate in loco de radiotherapia o chirurgia quando le duo morbos occurre in association.

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IDIOPATHIC RETROPERITONEAL FIBROSIS ASSOCIATED WITH A COAGULATION DEFECT (FACTOR VII DEFICIENCY): REPORT OF A CASE AND REVIEW OF THE LITERATURE *

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In 1948 Ormond [1] described two patients with bilateral hydronephrosis secondary to obstruction of the ureters by retroperitoneal fibrous tissue proliferation of unknown etiology. Since the original description by Ormond, 23 similar cases have been reported in the literature. The clinical manifestations are predominantly the result of ureteral obstruction, with subsequent hydronephrosis and renal infection, or insufficiency due to the involvement of the ureters in the retroperitoneal fibrous tissue reaction. The term "bilateral symmetrical periureteric fibrosis" was used by Raper [9] in 1955 to describe this syndrome, but subsequently this same author felt that "idiopathic retroperitoneal fibrosis" was a more suitable appellation.[10]

We have studied a patient with idiopathic retroperitoneal fibrosis, and a defect in blood coagulation due to a deficiency of Factor VII. The present report includes a description of this case, the results of an investigation of the coagulation defect, and a critical review of previously reported cases of idiopathic retroperitoneal fibrosis.

Case Report

This 25 year old Negro male, a laborer by occupation, was first admitted to the Louisville Veterans Administration Hospital on May 9, 1949, complaining of weight loss and lower abdominal pain of approximately three months' duration. Complete physical examination and laboratory studies were performed, including an upper gastrointestinal series and barium enema. The laboratory examinations were unremarkable, but a proctoscopic examination revealed the presence of a fixed, hard mass in the pelvis, anterior to the rectum, superior to and separate from the prostate. The patient refused permission for a biopsy, and left the hospital against medical advice.

He was re-admitted to the Veterans Administration Hospital on June 6, 1951, complaining of pain in the lower abdomen and bleeding from the rectum of approximately 18 months' duration. In addition to the pain in the lower abdomen, he had also noted pain in the left thigh, constipation, stools of decreased caliber, nocturia, urinary frequency and a diminished urinary stream. The pelvic mass was

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TABLE 1

Laboratory Studies, November, 1957

WBC	31,850	Cephalin floc.	3 plus in 24 hrs., 4 plus in 48 hrs.
Hb.	7.9 gm.		
Hct.	25%	Thymol turbidity	4.3 units
Urine—Reaction	Alkaline	Serum bilirubin	0.7 mg.%
Sp. gr.	1.016	Alkaline phos.	1.71 B. units
Albumin	3 plus	Total cholesterol	109 mg.%
Micro.	Numerous WBC, RBC, and bact.	Serum albumin	3.35 gm.%
		Serum globulin	2.35 gm.%
Urine culture	*Aerobacter aerogenes*, *Pseudomonas aeruginosa*, Gamma strep.	BSP	9% retention in 45 minutes
		VDRL	Nonreactive
		Red cell fragility	Normal
		Sickle cell prep.	Negative
Blood culture	*Aerobacter aerogenes*	Urine uroporphyrin and coproporphyrin	Negative
BUN	144 mg.%	Fasting blood sugar	86 mg.%
Creatinine	12 mg.%	Acid phosphatase	1.4 K-A units before alcohol deactivation
HCO_3	5.48 mEq./L.		
Na	150 mEq./L.		0.4 K-A units after alcohol deactivation
Cl	115 mEq./L.		
K	6.6 mEq./L.	Urine qual. 5 hydroxy-indoleacetic acid	Negative
Ca	4.27 mEq./L.		
P	4.66 mEq./L.		
Blood pH	7.14		

again demonstrated and was noted to have increased in size. A cystoscopic examination revealed evidence of extrinsic pressure on the prostatic urethra and trigone of the bladder. An exploratory laparotomy was performed, which revealed a diffuse area of firm, grayish white fibrous tissue on the posterior surface of the bladder, extending to the prostate and laterally along each pelvic brim to the region of the ureters. The rectum and sigmoid colon were not involved, but no distinct boundary to the fibrotic reaction was present. Multiple biopsies were obtained, and microscopic examination revealed the presence of dense fibrous tissue which resembled keloid. Profuse bleeding from the abdominal incision developed on the second postoperative day, and a laparotomy was required to control bleeding from the biopsy sites. The patient's prothrombin time was 18% of normal, and on subsequent determinations was found to range between 5% and 10%. The administration of large amounts of vitamin K produced no significant change. It was noted that he had not bled abnormally following a tonsillectomy in 1945 or multiple stab wounds in 1947, nor was there a familial history of bleeding. Other laboratory examinations, including blood coagulation studies, were not remarkable. The bleeding episode subsided following blood transfusions, and the remainder of his hospitalization was uneventful.

The patient was re-admitted to the Veterans Administration Hospital on October 10, 1954, complaining of progressive weakness of his arms and legs of six weeks' duration and, at the time of admission, was extremely weak and unable to walk without assistance. He also complained of intermittent pain in the left lower quadrant of the abdomen and the presence of bright red blood in the urine. On physical examination there were extreme weakness of all extremities, hypoactive deep tendon reflexes and moderate abdominal distention. The pelvic mass was

palpable on rectal examination and could not be differentiated from the prostate. Laboratory and radiographic studies revealed the following significant abnormalities: The urine had a fixed specific gravity of 1.007 and contained numerous red cells, white cells and bacteria. An intravenous pyelogram revealed moderate bilateral hydronephrosis. The prothrombin time was 5% of normal, and the serum potassium



FIG. 1. Intravenous pyelogram. Right hydronephrosis and decreased excretion of dye by left kidney.

was 2.2 mEq./L. The patient's weakness responded dramatically to potassium administration. No further urologic studies were performed on this admission, and he was discharged essentially asymptomatic.

The patient was re-admitted to the Veterans Administration Hospital on November 13, 1957, complaining of pain in the lower abdomen, blood in the urine and generalized weakness. At the time of his admission to the hospital he was

confused and unable to give an adequate history. Physical examination revealed a well developed, well nourished Negro male who appeared to be chronically and acutely ill. The temperature was 97° F. orally; pulse rate, 90 per minute; blood pressure, 130/88 mm. Hg; respiratory rate, 30 per minute. Significant features upon examination were as follows: There was a moderate pallor of the skin and mucous membranes. The gums were soft and spongy, and bled easily. The heart was enlarged to the left of the midclavicular line. There was a well healed midline surgical scar in the lower abdomen. The anterior abdominal wall was tense, and



FIG. 2. Barium enema. Narrowing of the rectosigmoid by extrinsic pressure.

there was generalized tenderness throughout the lower abdomen. The liver, spleen and kidneys were not palpated. The urinary bladder was grossly distended and was catheterized with difficulty. On rectal examination, a diffuse hard mass was palpable anterior to the rectum and the induration extended throughout the pelvis. The prostate could not be adequately outlined. The remainder of the physical examination, including a neurologic examination, was not remarkable. The laboratory findings are shown in table 1. The significant abnormalities were the presence of a prolonged prothrombin time, azotemia and acidosis. A urine culture was positive for *Aerobacter aerogenes*, and the same organism was cultured from the blood. A chest x-ray revealed moderate cardiomegaly. An electrocardiogram showed T wave

changes consistent with myocardial ischemia. Tuberculin tests in both strengths and a Frei skin test for lymphopathia were negative.

A cystoscopic examination performed by Dr. John Jurige revealed trabeculation of the bladder consistent with chronic obstruction and cystitis. The ureteral orifices



FIG. 3. Microscopic section of retroperitoneal tissue, showing fibrous tissue proliferation.

could not be identified, and the bladder neck was distorted and obstructed. Intravenous pyelography revealed a right hydronephrosis and decreased dye excretion by the right kidney (figure 1). The left kidney was not visualized. An upper gastrointestinal series was negative. A barium enema revealed narrowing of the

rectosigmoid from extrinsic pressure (figure 2). Planigraphic films of the pelvis showed bilateral increase in soft tissue density, greater on the left. The upper margin of the soft tissue density was lobulated and extended above the upper edge of the left ilium. A perineal needle biopsy of the prostate showed hyperplasia. A needle biopsy of the pelvic mass through the anterior wall of the rectum showed fibrous tissue proliferation, with areas of degeneration and moderate inflammatory cell infiltration. The biopsy specimen from the pelvic mass was identical with the specimens obtained by laparotomy in 1951 (figure 3). The results of blood coagulation studies are shown in table 2.

TABLE 2

Coagulation Studies

Bleeding time: 2½ min.

Coagulation time (Lee-White): 7 min.

Platelets: 312,000

Prothrombin consumption 93%
Prothrombin time
Normal 10–12 sec.
Patient 15–21 sec.

Two-stage prothrombin (Ware and Seegar):
Prothrombin concentration 50%

Russell's viper venom (Stypven time):
Normal 13–19 sec.
Patient 14 sec.

Correction studies—one-stage prothrombin time:
Normal 11 sec.
Patient 17 sec.
90% patient's plasma + 10% serum 13 sec.
90% patient's plasma + 10% $BaSO_4$ plasma 16.5 sec.
90% patient's plasma + 10% Christmas disease serum 14 sec.
90% patient's plasma + 10% stored oxalate plasma 13 sec.

Thromboplastin generation test:
Normal

It was felt that the clinical findings and histologic evidence were consistent with a diagnosis of idiopathic retroperitoneal fibrosis, as described by Ormond. Foley catheter drainage was instituted because of the obstruction at the bladder neck, and the bacteremia was cured and the urinary tract infection improved following antibiotic therapy. The acidosis and azotemia gradually improved. An intravenous pyelogram seven weeks after the first study revealed bilateral hydronephrosis and excretion of the dye by both kidneys. Following recovery from his acute illness, the patient became asymptomatic.

DISCUSSION

The patient described herein is similar to previously reported cases of idiopathic retroperitoneal fibrosis except for the fact that the fibrous tissue proliferation was not confined to the periureteric area, but apparently arose in the region of the bladder neck and subsequently extended to involve the ureters, prostate and rectosigmoid. A review of the available literature revealed 23 cases of idiopathic retroperitoneal fibrosis with ureteric compression, in addition to the two reported by Ormond in 1948.[1] The pertinent data concerning these cases are outlined in table 3. The age of the patients at the onset of symptoms

TABLE 3

Summary of the Previously Reported Cases of Idiopathic Retroperitoneal Fibrosis, Each Confirmed by Surgery or at Autopsy

Author—Date Reported	Case No.	Sex—Age at Onset of Symptoms	Race	Clinical Features	Pathology	Treatment	Condition at Time of Report
Ormond,[1] 1948	1	Male—45 yrs.	W	Bilateral hydronephrosis; anuria; azotemia; anemia; ache in back and thighs; chronic urinary tract infection	Autopsy: fibrous retroperitoneal mass covered promontory of sacrum, with envelopment and compression of ureters; microscopy: fibrous connective tissue	Frequent ureteral dilatation	Patient died
Ormond,[1] 1948	2	Male—40 yrs.	W	Bilat. hydronephrosis; anuria; anemia; backache	Similar gross and microscopic findings	Ureterolysis with postop. deep x-ray therapy	Excellent
Ewell and Bruskewitz,[2] 1952	3	Male—49 yrs.	Not given	Bilat. hydronephrosis; anuria; pain in left flank and abdomen; medial deviation of ureter	Bilat. perirenal fibrosis, with right ureter encased in fibrous thickened fat; biopsy: inflammation and fibrosis, with an acute arteriolitis	Left nephrectomy; rt. ureteral catheter drainage, followed by nephrectomy and ureterolysis	Good
Oppenheimer et al.,[3] 1952	4	Male—55 yrs.	W	Right hydronephrosis; hematuria; pain in right pubic area	Inflammatory mass surrounded lower right ureter; biopsy: inflammatory tissue	Exploration with T tube drainage of rt. ureter; later, x-ray therapy	Excellent
Miller et al.,[4] 1952	5	Male—53 yrs.	N	Palpable mass in mid-abdomen; bilat. hydronephrosis; anuria; azotemia; anemia; pain in left flank, testicle and thigh	Retroperitoneal mass extended from the kidneys down over the sacrum, with embedded ureters; biopsy: subacute inflammation	Exploratory with biopsy only; antibiotics	Good
Miller et al.,[4] 1952 (Amselem, 1950)	6	Female—23 yrs.	W	Bilat. hydronephrosis; uremia: anemia; pain in rt. hypochondrium	Incomplete report: "adhesions" around left ureter, found at surgery	Bilat. nephrostomy, followed by rt. nephrectomy and left ureterolysis	Good
Miller et al.,[4] 1952 (Helfert)	7	Male—41 yrs.	W	Oliguria; uremia and acidosis, improved by ureteral catheterization	Constriction of rt. kidney by indurated adipose tissue; biopsy: severe inflammation	Right nephrolysis	Good
Mirabile and Spillane,[5] 1953	8	Female—34 yrs.	Not given	Bilat. hydronephrosis; anuria; azotemia; anemia; hypertension; pain in left flank	Both ureters surrounded by an inflammatory process; resected portion of left ureter revealed scarring and chr. inflammatory reaction	Ureteral catheter drainage and antibiotics; bilat. ureterolysis; left ureteral segmental resection with anastomosis	Good
Bradfield,[6] 1953	9	Male—51 yrs.	W	Bilat. hydronephrosis; pain in back, lower abdomen and testicles; weakness	Both ureters surrounded by a mass of indurated tissue lying over the promontory of the sacrum; biopsy: chr. inflammation	Ureteral catheter drainage; left nephrostomy with postop. x-ray therapy; later, bilateral ureterolysis	Good
MacLean,[7] 1954	10	Male—24 yrs.	Not given	Left hydronephrosis; pain in left flank, back and hips	Left ureter densely bound down in the area of the iliac vessels	Exploration with left ureterolysis	Good

TABLE 3—*Continued*

Author—Date Reported	Case No.	Sex—Age at Onset of Symptoms	Race	Clinical Features	Pathology	Treatment	Condition at Time of Report
Chisholm et al.,[8] 1954	11	Male—36 yrs.	W	Ulcerative colitis for 11 yrs.; dependent edema; bilat. hydronephrosis; impotence; anemia; azotemia	Both ureters obstructed and displaced medially by a thick fibrous sheath from level of kidneys to promontory of the sacrum; biopsy: chr. inflammatory tissue	Bilat. nephrostomy and ureterolysis	Good
Raper,[9] 1955	12	Female—25 yrs.	Not given	Bilat. hydronephrosis with medial deviation of both ureters and obstruction of left ureter; azotemia; abdominal colic; enlarged left kidney	Both ureters bound down by fibrous tissue; biopsy: marked fibrosis with cellular infiltration and calcification	Bilat. ureterolysis with left ureteral segmental resection and anastomosis	Not stated
Raper,[9] 1955	13	Male—45 yrs.	Not given	Both ureters blocked and deviated medially; azotemia; pericarditis and duodenal ulcer; pain in flank areas	Both ureters involved in an inflammatory process lying anterior to the vertebral bodies, with obliteration of the right ureter near the bifurcation of the iliac vessels	Left ureterolysis with a nephrostomy later; right ureteral segmental resection with anastomosis	Good
Raper,[9] 1955	14	Female—41 yrs.	Not given	Bilat. hydronephrosis; anuria 17 days postop. after gyn. surgery; pain in left flank	Upper left ureter surrounded by scar tissue and adherent to the vertebral bodies	Left nephrostomy	Died 24 hrs. after surgery, probably because of high serum potassium
Raper,[10] 1956	15	Female—53 yrs.	Not given	Bilat. hydronephrosis with atrophic left kidney; azotemia; backache	Both ureters encased in a tunnel of dense fibrous tissue from L3 to just beyond the pelvic brim	Bilateral ureterolysis	Fair
Raper,[10] 1956	16	Male—43 yrs.	Not given	Intermittent obstruction of ureters with oliguria and anuria; azotemia; anemia; pain in back and flank areas; jaundice	Autopsy: fibrous plaque extended from crura of diaphragm almost to the top of the seminal vesicles, surrounded the ureters and obstructed the common bile duct	Rt. nephrectomy; intermittent therapy with sulfa and transfusions; left nephrostomy attempted, incomplete	Died, apparently from renal failure
Case Records of the Mass. Gen. Hosp.,[11] 1956	17	Male—64 yrs.	Not given	Bilat. ureteral obstruction; anuria; azotemia; anemia	Right upper and left lower ureter embedded in dense, firm tissue; biopsy: inflammatory fibrous-fatty tissue	Bilat. ureterolysis and nephrostomy	Good
Case Records of the Mass. Gen. Hosp.,[12] 1957	18	Male—56 yrs.	Not given	Left hydronephrosis with medial deviation of the ureter; pain in lower abdomen, left flank and hip; weight loss	Upper abdominal mass arose behind the pancreas, extended over the lumbar vertebrae and involved the left ureter; biopsy: inflammatory fibrosis	Exploration and biopsy, with subsequent left ureterolysis	Not stated
Iozzi and Murphy,[13] 1957	19	Male—44 yrs.	W	Bilat. alternating hydronephrosis; pain in abdomen and flank areas; weight loss; constriction of rectosigmoid colon	Envelopment of both ureters and rectosigmoid in extensive mass of indurated fibrous tissue; biopsy: chronic inflammatory fibrofatty tissue	Left ureterolysis and nephrostomy; right ureterolysis; proximal colostomy	Excellent

TABLE 3—*Continued*

Author—Date Reported	Case No.	Sex—Age at Onset of Symptoms	Race	Clinical Features	Pathology	Treatment	Condition at Time of Report
Talbot and Mahoney,[14] 1957	20	Male—40 yrs.	W	Resembled nephritis, with hypertension, urinary findings, azotemia, anemia, and pain in back and flank areas; found to have bilat. hydronephrosis (intermittent on left)	Right ureter and right iliac vessels enveloped by a mass of dense fibrous tissue; biopsy: dense fatty fibrous tissue	Right ureterolysis and T tube drainage, followed by right nephrostomy and antibiotics	Excellent
Trever,[15] 1958	21	Male—51 yrs.	Not given	Constriction of rectosigmoid colon; regional lymphadenopathy, with edema of lower abdomen and left leg; bilat. hydronephrosis; pain in low back and lower abdomen; partial small bowel obstruction	Extensive fibrosis surrounded the rectosigmoid colon, both ureters and left ext. iliac vessels; later it was found to involve the mesentery of the bowel and retroperitoneal space; biopsy: proliferating connective tissue; reticulum cell sarcoma in mesenteric lymph nodes	Sigmoid colostomy; bilat. partial ureterolysis with nephrostomy; lysis of abdominal adhesions; nitrogen mustard	Good
Case Records of the Mass. Gen. Hosp.,[16] 1958	22	Male—59 yrs.	Not given	Right hydronephrosis; discomfort in right back, abdomen and right testicle	Right ureter involved at the upper margin of the sacrum in a firm retroperitoneal mass which crossed the midline and extended over the great vessels; biopsy: dense fibrosis with invasion of ureteral muscular wall	Right nephrectomy with excision of ureter	Not stated
Mulvaney,[17] 1958	23	Male—50 yrs.	Not given	Bilat. hydronephrosis; azotemia; anemia; hypertension; weight loss; recurrent pyuria; back and abdominal pain	Extensive dense fibrous mass surrounded segment each ureter; biopsy: nonspecific inflammatory reaction. Left kidney destroyed by infection	Rt. ureterolysis with ureteral segmental resection and anastomosis; left nephrectomy	Good
Mulvaney,[17] 1958	24	Female—43 yrs.	Not given	Bilat. hydronephrosis; azotemia; anemia; urinary tract infection; hypertension; bilat. flank and abdominal pain	Right ureteral involvement by fibrous mass identical with the preceding case	Right ureterolysis and nephrostomy; left nephrostomy	Died of uremia one week postop.
Mulvaney,[17] 1958	25	Female—21 yrs.	Not given	Right hydronephrosis with recurrent right pyelonephritis	Same as preceding case	Right ureterolysis with segmental resection and anastomosis	Good

ranged from 21 to 64 years, with the greatest incidence in the fourth decade. The data are not sufficient to determine any racial predilection, but the majority are of the white race, and males predominate over females in a 4:1 ratio.

The etiology of retroperitoneal fibrosis is unknown. Although the pathologic changes are consistent with a low grade inflammatory reaction, a definite association with infection has not been proved. The involvement of the rectum which was present in our case suggested lymphopathia venereum as a possible cause, but the negative Frei test, the absence of buboes and the fact that lymphopathia does not extend beyond the perirectal area seemed to exclude this diagnosis. Retroperitoneal fibrosis secondary to retroperitoneal hemorrhage was suggested by the coagulation defect. Retroperitoneal bleeding is not uncommon in hemophilia, but extensive retroperitoneal fibrosis with distortion of retroperitoneal structures has not been described, and it seems unlikely that retroperitoneal hemorrhage produced the changes observed. We have observed fibrosis of the retroperitoneal tissue in a patient with the carcinoid syndrome, and since the fibrotic reaction qualitatively resembled the changes observed in idiopathic retroperitoneal fibrosis, it seemed worth while to exclude an abnormality of tryptophan metabolism in our patient. A qualitative determination of 5 hydroxyindoleacetic acid in the urine was negative. Trever [15] has reported a case, initially thought to have idiopathic retroperitoneal fibrosis, in whom a reticulum cell sarcoma was demonstrated in a mesenteric lymph node after repeated laparotomies. This author emphasized the necessity of obtaining multiple biopsies from the retroperitoneal fibrous tissue reaction before the process should be considered idiopathic. The long history and benign course in our patient make neoplasia extremely unlikely.

The pathologic lesion is remarkably similar in the previously reported cases, as noted in table 3. In the majority the process arises in the retroperitoneal area near the bifurcation of the aorta and promontory of the sacrum, and may extend throughout the retroperitoneal area from the floor of the pelvis to the dome of the diaphragm. The ureters become surrounded and embedded in the dense fibrous tissue, and hydronephrosis results, but the ureters are not invaded by the fibrous tissue. Both ureters are usually involved, and unilateral involvement is thought by some to represent disease of brief duration. Hydronephrosis has been noted in the absence of extrinsic obstruction, apparently from a loss of ureteral tone. Grossly, the fibrotic tissue appears to be grayish white in color, with indistinct borders, and microscopically consists of dense connective tissue with a varying degree of infiltration by lymphocytes and round cells, but the predominant cellular reaction is fibroblastic proliferation.

The clinical manifestations of idiopathic retroperitoneal fibrosis are pain in the lower abdomen, back or flank, symptoms due to infection of the urinary tract, and uremia. Pain varying in location and severity has been described in 20 of the 25 previously reported cases, and in some instances pain has preceded the manifestations of urinary tract involvement. Nine of the patients of this series developed oliguria or anuria, and 14 became uremic (table 3).

The diagnosis of idiopathic retroperitoneal fibrosis should be considered in any patient who presents with hydronephrosis without obvious cause, and particularly when ureteral obstruction is due to extrinsic pressure. The most common extrinsic cause of ureteral obstruction is neoplasia, including the lymphomas. Retroperitoneal neoplasms generally cause marked distortion of

the ureter, with lateral and anterior displacement with minimal compression, whereas idiopathic retroperitoneal fibrosis produces marked narrowing and compression of the ureters with slight medial displacement. The diagnosis cannot be established, however, without a complete urologic investigation and pathologic examination of the retroperitoneal tissue.

The methods of treatment used in the previously reported cases are briefly outlined in table 3. The primary concern is to promote adequate urinary flow and relief of obstruction if possible. All cases of this series had some type of surgical procedure designed primarily to relieve the obstruction of the ureters. Conservation of renal tissue is of the utmost importance, since involvement is frequently bilateral, and an ill advised nephrectomy may accelerate the onset of uremia. X-ray therapy directed at the fibrous tissue has been utilized in three cases, with excellent results in two.[1, 3] Antibiotics have been used to control infection of the urinary tract, without having any effect on the fibrous tissue proliferation. To our knowledge, steroids have not been utilized in the treatment of idiopathic retroperitoneal fibrosis.

The principal laboratory abnormality indicative of a coagulation defect in our patient was a prolonged one-stage prothrombin time. Prolongation of the one-stage prothrombin time may result from a deficiency of prothrombin, of the prothrombin accelerators Factor V and Factor VII, or the recently described Stuart factor, by hypofibrinogenemia, or by a circulating anticoagulant.[18, 19] A summary of the coagulation studies performed is given in table 2, and detailed observations concerning the coagulation defect will be published elsewhere. The prolonged prothrombin time was shortened by the addition of normal serum, and was normal when Russell's viper venom (Stypven) was used as a source of thromboplastin. Barium sulfate-absorbed plasma, which contains Factor V and no Factor VII, did not shorten the prolonged prothrombin time. The addition of serum from a patient with Christmas disease resulted in a shortening of the prolonged prothrombin time. These results are characteristic of and consistent with a deficiency of Factor VII.[20] The quantitative determination of prothrombin by the two-stage method revealed a concentration of 50%, but the reduction of prothrombin probably did not contribute significantly to the coagulation defect. The prothrombin time was shortened by the addition of normal serum, which does not contain prothrombin, and a reduction in the concentration of prothrombin of this magnitude does not produce a prolongation of the prothrombin time.[21] A deficiency of Factor V was excluded by the failure of barium sulfate-absorbed plasma to correct the one-stage prothrombin time, and a circulating anticoagulant excluded by the correction of the one-stage prothrombin time by the addition of normal plasma. Fibrinogen was not quantitatively assayed, and hypofibrinogenemia was excluded by the character of the clot and the corrective effect of serum. Stuart factor deficiency was excluded by the normal thromboplastin generation test and the presence of a normal prothrombin time when Russell's viper venom was used as a source of thromboplastin.

The genesis of the deficiency of Factor VII and its relationship to the retroperitoneal fibrosis are obscure. The majority of the previously reported cases of Factor VII deficiency represent congenital deficiencies of this factor and have prolonged histories of abnormal bleeding.[20] Our patient had had no abnormal bleeding until 1951, when hemorrhage occurred following a laparotomy,

and there was no family history of abnormal bleeding. Despite the absence of bleeding episodes prior to the onset of his illness in 1951, we believe the coagulation defect in our patient represents a mild congenital deficiency of Factor VII. It would of course be of fundamental interest to relate the coagulation defect to the retroperitoneal fibrosis, and the possibility of spontaneous retroperitoneal hemorrhage with subsequent fibrosis has been mentioned. It is important to point out, however, that spontaneous bleeding was not a significant feature in our patient, and that the only overt evidence of bleeding followed a major surgical procedure. The most recent episode of bleeding was manifested as hematuria, and was associated with pyelonephritis and renal insufficiency, and at no time were petechiae, ecchymoses, epistaxis or other evidence of spontaneous bleeding noted.

The administration of vitamin K as vitamin K_1 oxide had no effect on the prolonged prothrombin time. The concomitant administration of vitamin K_1 oxide and methionine has been reported to be of value in correcting the coagulation defect in patients with a deficiency of the prothrombin accelerators Factor V and VII, but this combination produced no change in our patient.[22]

Finally, it is our opinion, based on the features of the case reported herein, that the term "periureteric" is a misnomer, since the retroperitoneal fibrosis may not be confined to the periureteric area, and may be associated with actual tumor masses. We believe that the term "idiopathic retroperitoneal fibrosis" is more suitable.

Summary

A case is reported of idiopathic retroperitoneal fibrosis associated with a coagulation defect characterized by a deficiency of Factor VII. The previously reported cases of idiopathic retroperitoneal fibrosis are reviewed, and studies concerning the coagulation defect are presented.

Summario in Interlingua

Es presentate le aspectos clinic del caso de un masculo negre de 25 annos de etate con hydronephrosis bilateral secundari a obstruction del ureteres per tissu fibrose retroperitoneal. Le constatationes es de accordo con un syndrome primo describite per Ormond sub le termino de "idiopathic fibrosis periureteric." Es revistate le previemente reportate casos de iste syndrome. Le major manifestationes clinic es secundari a obstruction ureteral e es characterisate per dolores dorsal o infero-abdominal, oliguria, e uremia. Le etiologia del proliferation de tissu fibrose non es cognoscite. Le rolo possibile de infection, hemorrhagia, e neoplasia es discutite super le base del hic-presentate caso. Le reaction de tissu fibrose non esseva restringite al area periureteric. A causa de isto, le termino idiopathic fibrosis retroperitoneal esseva considerate como plus appropriate que le termino idiopathic fibrosis periureteric.

A parte le fibrosis retroperitoneal, le patiente hic describite habeva un defecto coagulatori characterisate per un carentia de Factor VII. Le studios de coagulation le quales estabiliva le diagnose de carentia de Factor VII es presentate. Le diagnose laboratorial de iste defecto coagulatori e su connexion con le fibrosis retroperitoneal es discutite. Super le base del studios clinic e laboratorial le assertion pare justificate que iste patiente ha idiopathic fibrosis retroperitoneal associate con un congenite carentia de Factor VII.

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THROMBOCYTOPENIA ASSOCIATED WITH THE ADMINISTRATION OF DIETHYLSTILBESTROL IN MAN *

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Estrogen administration has been reported to cause aplastic anemia in dogs,[1, 2, 3] and in man has been associated infrequently either with hypoplastic anemia and thrombocytopenia,[4, 5] or with purpura without thrombocytopenia.[6, 7] In the case reported below, oral administration of diethylstilbestrol was promptly followed by thrombocytopenia and pruritus. The rarity of this sequence prompts this case report.

Case Report

A thin, 88 year old white male entered the Boston City Hospital in November, 1957, for therapy of leg ulcers. Perineal prostatectomy had been performed one year previously for asymptomatic adenocarcinoma of the prostate. Physical examination was unremarkable except for 1° to 2° F. of fever, infected superficial excoriations on both legs, and a hard nodule in the region of the prostate. Admission blood studies revealed a hematocrit of 38%, a white blood cell count of 7,000 per cubic millimeter, with normal differential, and adequate platelets on smear. Serum acid and alkaline phosphatase determinations and x-rays of the bones were normal.

The leg ulcers healed on conservative therapy and fever abated. After bilateral orchiectomy, administration of oral diethylstilbestrol, 5 mg. twice a day, was begun. Two weeks thereafter the patient developed marked pruritus of the legs as well as leukopenia and thrombocytopenia. White blood cell counts varied from 2,000 to 5,000 per cubic millimeter, with normal differential, while platelets were 64,000 per cubic millimeter. There was no purpura. Bone marrow aspiration at this time showed active erythropoiesis, myelopoiesis, and abundant normal megakaryocytes. Serum proteins were normal on electrophoretic examination. The medication was discontinued, with prompt disappearance of the pruritus and, during the following month, a gradual rise of the platelet count to 250,000 per cubic millimeter. The leukocyte count, however, remained low (2,500 to 4,500 per cubic millimeter) throughout the patient's ensuing hospitalization.

Test doses of diethylstilbestrol were administered orally on three additional occasions, during and after each of which rather prompt thrombocytopenia developed (figure 1). Direct platelet counts were performed daily. No change in leukocyte count, hemoglobin concentration or reticulocyte percentage occurred, and no purpura was noted. During the third administration of diethylstilbestrol a pruritic, maculopapular eruption appeared on the patient's legs, and disappeared after medication was discontinued. Bone marrow aspirated after the third course of drug administration, while thrombocytopenia was still present, was normal, with abundant megakaryocytes and platelet formation. Platelet agglutinins were sought in siliconized

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glassware by mixing the patient's serum with an equal volume of a platelet-rich preparation of normal plasma rendered incoagulable with Sequestrene.* This mixture was incubated for one hour at room temperature, with and without added diethylstilbestrol, to a final concentration of 0.01 mg. per milliliter, and thereafter wet cover-slip preparations were examined by phase contrast microscopy. By this method, no platelet agglutinin was demonstrable in the patient's serum before, during or after the oral administration of the drug.

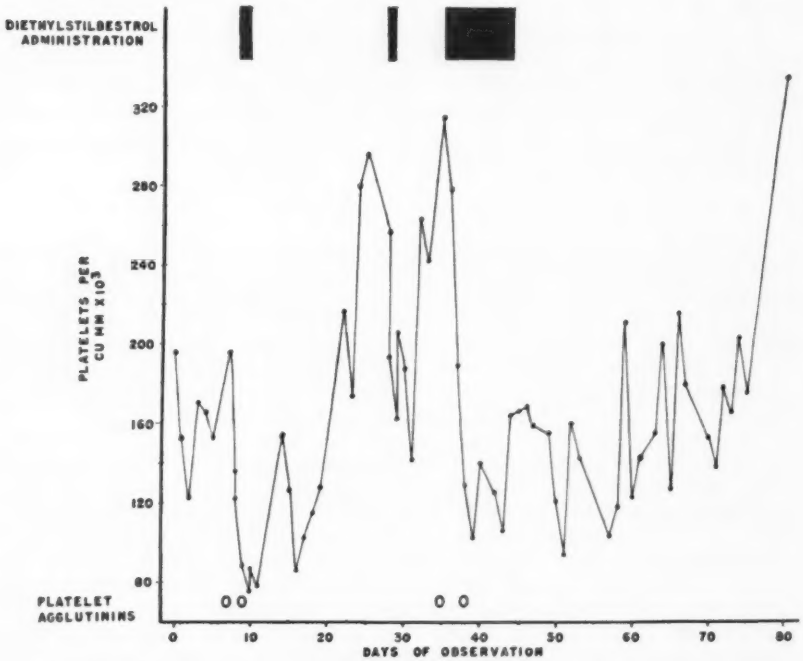


FIG. 1. The variation in direct platelet counts in venous blood with three administrations of oral diethylstilbestrol. The first administration was of 15 mg. over a period of 36 hours, the second was of 10 mg. in one dose, and the third was of 5 mg. twice daily for nine days. Between the fifteenth and twenty-first days the patient had lobar pneumonia, and was treated with penicillin. The zeros below the graph indicate the days on which serum platelet agglutinins were sought but not found.

DISCUSSION

As far as we are aware, clear documentation of recurrent, transient thrombocytopenia developing on repeated administration of diethylstilbestrol has not previously been reported. The persistence of the platelet count at levels as high as 100,000 per cubic millimeter despite administration of the drug for nine days (figure 1, third administration), together with the failure to demonstrate serum platelet agglutinins, with or without added drug, suggests a difference in the mechanism of the diethylstilbestrol effect on platelets from that of quinidine [8] and Sedormid.[9] Although not evident in the marrow aspirates,

* Alrose Chemical Co. brand of di-sodium ethylenediaminetetra-acetic acid.

subtle depression of marrow function seems to us a more probable explanation for the thrombocytopenia than does platelet sequestration. Such an action would be analogous to the marrow aplasia of estrogen-treated dogs,[1, 2, 3] and might explain the more than three weeks' delay in restoration of platelets to normal following the third administration of diethylstilbestrol.

Summary

Four episodes of temporary thrombocytopenia associated with oral diethylstilbestrol administration are reported in a patient with prostatic carcinoma.

Summario in Interlingua

Diethylstilbestrol esseva administrate a un patiente mascule de 88 annos de etate in le tractamento de adenocarcinoma que pareva esser localisate al prostata. Post un curso de duo septimanas de 5 mg del droga per die, prurito occurreva, e le numerationes plachettal e leucocytic descendeva significativemente. Le medulla non exhibiva ulle deviation ab le norma. Ben que le valores normal del plachettas e leucocytos se restabliva promptemente post le discontinuation del therapia, thrombocytopenia esseva re-effectuate a tres occasiones subsequente per le administration de diethylstilbestrol. Effortios de demonstrar un agglutinina de plachettas in vitro esseva sin successo al culmine del thrombocytopenia, si o non diethylstilbestrol esseva addite al systema del experimentation.

Ben que hypoplasia del medulla, con anemia e thrombocytopenia, se trova reportate sporadicamente como sequella al administration de diethylstilbestrol, recurrente thrombocytopenia in repetite cursos therapeutic—sin alteration morphologic del medulla e sin alteration del concentration de hemoglobina—ha non previemente essite describite. Le mechanismo del thrombocytopenia in iste caso es controverse.

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PACHYMENINGITIS APPARENTLY DUE TO PENICILLIN HYPERSENSITIVITY *

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Clinical and experimental observations [1-10] have established that protracted allergic reactions to drugs and foreign proteins may result in a variety of inflammatory and necrotizing tissue lesions. Such lesions, due to hypersensitivity to sulfonamides, penicillin, iodine, foreign sera and egg albumin, have been demonstrated mainly in the heart, lungs, kidneys, liver and spleen. In a patient under our observation there developed a marked pachymeningitis of the dura mater over both cerebral hemispheres, and a severe scleritis, apparently the result of an allergic reaction to penicillin.

Case Report

A 47 year old woman suffering from excruciatingly severe, unrelenting headache was admitted to Lenox Hill Hospital on December 9, 1955, to the care of Dr. Francis Echlin.

In 1945 the patient, who until then had been in generally good health, had suffered from dermatitis of the scalp and neck. In 1949 she had had dysuria associated with pyuria, for which she was treated with sulfadiazine. She was also given one injection of penicillin.

In the spring of 1954 the patient developed a rhinorrhea that was unresponsive to local therapy as well as to treatment with antihistaminics. The nasal condition persisted during the summer, and on August 13 she was given an injection of penicillin. Ten days later she developed generalized, severe giant urticaria and polyarthralgia, which subsided under vigorous treatment in three days.

On November 17 the patient experienced a sudden sharp pain in the left eye which appeared to be "bloodshot." A diagnosis of scleritis was made. This had a stormy course for one year. There were repeated flare-ups, and the patient was hospitalized three times because of severe ocular pain, periorbital edema, especially on the left, and chemosis. During this time keratitic precipitates developed, and there was impending loss of vision. Despite intensive treatment with antibiotics, sulfa drugs, salicylates, antihistaminics, steroids, artificial fever, sinus washings, autovaccines and tonsillectomy, there was progressive deterioration.

Early in October, 1955, the patient began to complain of occipital headaches, vertigo, tinnitus and mild deafness. On November 19 she had severe angio-edema. A week later there were a renewed flare-up of the ocular symptoms and an intensification of the occipital headache. The patient was admitted to Lenox Hill Hospital at the beginning of December for further study.

Physical examination showed the patient to be a well developed, well nourished middle aged female who, although oriented and alert, was apprehensive and in severe distress from unrelenting, excruciating head pain. Temperature, 99.4° F.; pulse, 84; respiration, 20; blood pressure, 98/58 mm. Hg. There were marked periorbital

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edema and proptosis. The bulbar conjunctiva of the left eye was densely injected, the pupil dilated. The fundus of the left eye was obscured by diffuse vitreous opacities, and there was severe amblyopia of this eye. The left ocular bulb was enlarged to twice the normal size and was tense and tender. Funduscopy of the right eye revealed 4 plus papilledema with flame-shaped hemorrhages and perivascular exudates. Weak bilateral abducens palsy was noted. The other cranial nerves appeared to be intact. The remainder of the physical and neurologic examination was not remarkable.

Laboratory Data: Hemoglobin, 11.6 gm.; white blood cell count, 8,750; differential count: 87 polymorphonuclears, 7 bands, 12 lymphocytes, 1 monocyte and a few atypical lymphocytes. Urinalysis, normal. Sedimentation rate, 110 mm.

Spinal fluid pressure (initial), over 600 mm. Glucose, 77 mg.%; protein, 41 mg.%; sodium chloride, 708. Cells per cm^2: 4 red blood cells, 21 white blood cells, of which 96% were lymphocytes and 4% polymorphonuclears. Routine smear: no organisms seen; smear for tuberculosis, negative. No growth on culture.

Blood serum: sodium, 137; potassium, 3.5; chlorides, 94.8; CO_2 capacity, 29.1 mEq./L. Blood serology: Mazzini, Kline negative.

X-ray examination of the skull showed decalcification of the posterior clinoids; the pineal gland was in the midline. Chest x-ray was normal.

The electroencephalogram showed a diffuse bilateral disorganization of the normal rhythms by slow waves of moderate voltage at 4 to 7 per second over all head regions, more dominant over the left frontotemporal area.

Clinical Course: On the third hospital day, bilateral occipital burr holes were made and a ventriculogram was carried out. The latter was interpreted as being normal. At operation the brain was under considerable pressure, the gyri were flattened, and spinal fluid escaped from the ventricular needle under increased pressure. The dura mater on the right was about three times its normal thickness. On the fifth hospital day the patient was very drowsy and aphasic. An emergency bilateral subtemporal exploratory craniectomy was performed. The dura was found to be markedly thickened in each temporal region (about ¼ to ⅓ inch thick). On its outer surface it was yellowish and avascular, on its inner surface softer and pinker. There was no evidence of any subdural hematoma on either side, and the underlying brain appeared to be normal, although under increased pressure. *Microscopic examination* by Dr. Rudolf M. Paltauf of biopsied specimens of the dura showed large amounts of organized, or hyalinized, exudate bordered by granulation tissue which in areas was poorly vascularized and infiltrated with inflammatory cells of various types, including multinucleated giant cells. No caseation necrosis or tubercle formation was observed. The blood vessels showed no evidence of periarteritis nodosa. A diagnosis of "granulomatous chronic pachymeningitis" was made.

Following the operation the headaches were somewhat relieved, but almost daily lumbar punctures were required to control the pain. On the seventeenth hospital day the initial spinal fluid pressure was 270 mm. The glucose content of the spinal fluid was 77 mg. %, the protein content, 49 mg. %. Repeated cultures of the spinal fluid on special media, including chocolate agar and Sabouraud's medium, cultures and guinea pig inoculations for tuberculosis, were negative. Three serial examinations of the blood for L.E. cells were also negative. After three weeks of hospitalization there was no improvement in the patient's condition. The headaches, the ocular pain, the proptosis and the amblyopia persisted. The objective eye findings were the same as on admission. The brain herniation through the bilateral decompression areas produced elevations of at least 1 cm. beyond the skull. The patient's temperature, which had risen to 103° F. postoperatively fluctuated between 100° and 102° F., although she was being maintained on broad-spectrum antibiotics.

On reëvaluation of the patient's history and the course of her illness at this point, it was felt that her ocular and meningeal pathology was possibly due to allergic inflammation. The severe attack of urticaria 10 days after a repeat injection of penicillin, the onset three months later of scleritis of unknown etiology followed by pachymeningitis, the increased sedimentation rate, the absence of evidence of infection, all suggested allergy as a possible basis of the patient's symptomatology. A specimen of the dura, taken at operation on December 13, 1955, was submitted to Dr. William Ehrich* and evaluated by him as follows: "Microscopic examination reveals several pieces of dura showing extensive swelling and necrosis of dense collagenous connective tissue surrounded by inflammatory granulation tissue rich in fibroblasts and plasma cells. The necrosis is characterized by the presence of numerous small bodies staining blue with hematoxylin. These resemble disintegrating nuclei. The granulation tissue forms poorly outlined granulomas in places such as seen in collagen diseases. Some of these contain neutrophiles and eosinophiles. Also present are occasional foam cells and giant cells some of which are multinucleated. The walls of several vessels are markedly swollen, but no vascular necrosis is found. There is no evidence of tuberculosis or of any other specific inflammatory process in these sections.

"The abundance of plasma cells in this lesion leaves little doubt that antibodies were formed locally. These together with the eosinophiles seem to indicate that allergy was a significant component of this reaction. The cause of the allergy is not apparent. No microörganisms or fungi could be demonstrated."

Treatment with corticotropin was instituted on the twenty-ninth hospital day, the patient receiving 100 units of ACTH gel a day. Within 24 hours her excruciating headache and eye pain abated, and within a few days they became almost negligible. The temperature dropped to below 100° F. and remained between 98.8° and 99.8° F. except for two days when it reached 100.2° and 100.4° F. The sedimentation rate decreased from 110 mm./hr. preoperatively to 5 mm./hr. on the twentieth day of corticotropin therapy. In the following weeks it fluctuated with the amount of hormone given. The dosage of ACTH was tapered off and the medication was gradually changed to Meticorten. On a maintenance dose of 40 mg. a day the erythrocyte sedimentation rate was 10 mm. ± 4 mm.

The herniation through the temporal burrholes and the papilledema of the right eye decreased considerably. The vitreous opacities in the left eye began to clear and it became possible to obtain glimpses of the fundus of the left eye. Within a month there was some return of vision in this eye.

The spinal fluid pressure decreased postoperatively. Five days after operation it was 440 mm. (initial); on the ninth postoperative day it was 220 mm. There was no further appreciable diminution of the pressure after institution of steroid therapy.

The patient was discharged from the hospital on April 12, 1956, and maintained on 40 mg. of Meticorten a day. She was continued on a diet free from milk and milk products which had been instituted as a precautionary measure in view of the now so frequently encountered penicillin content of milk.

Subsequent Course: The patient became ambulatory at home but was unable to work. Headaches were transitory. Vision in the left eye remained very poor. The sedimentation rate continued to be normal, the spinal fluid pressure remained slightly elevated, and there was intermittent slight bulging of the subtemporal decompressions. Papilledema in the right eye remained absent.

During the spring and summer of 1956 Meticorten was tapered off. In November the patient was able to resume her usual work almost full-time.

No hypertension, glycosuria, obesity or hirsutism resulted from the protracted steroid therapy. A moon facies, a buffalo hump and gastrointestinal complaints did supervene, however. Also, severe demineralization of the spine was found after

* University of Pennsylvania, Graduate School of Medicine.

10 months, and there were painless collapses of a lower thoracic and of a high lumbar vertebra.

During the summer of 1957 the patient started having generalized body aches and marked fatigue. When the steroids were increased the pains became more severe. On October 12 the patient was hospitalized because of excruciating pain in the lower legs. Steroids were withdrawn and the acute picture subsided. There was no clinical or laboratory evidence of recurrence of central nervous system or ocular involvement. Steroid therapy has not been resumed. The patient is now (January, 1960) fully employed.

Comment

Inflammation of the dura mater is in most instances due to infection. In the case under discussion, pertinent examinations failed to elicit infection as the cause of the pachymeningitis. On the other hand, the sequence of clinical events, the histologic appearance of the dura and the result of treatment with ACTH and corticosteroids strongly suggest allergy as the cause of the dural inflammation.

Summary

Ten days after receiving an injection of penicillin a 47 year old woman experienced a severe, serum sickness-like reaction. Three months later she developed scleritis of unknown etiology which resisted all forms of therapy and which was followed after another 11 months by the signs and symptoms of increased intracranial pressure. At operation (bilateral subtemporal exploratory craniectomy), the patient's dura was found to be greatly thickened (¼ inch to ⅓ inch). Microscopic examination of biopsied specimens of the dura suggested an allergic inflammation. Intensive treatment with ACTH and corticosteroids led to regression of the patient's clinical symptoms.

Summario in Interlingua

Dece dies post reciper un injection de penicillina—cinque annos retro le sol previe tal injection habeva essite administrate—un patiente feminin de 47 annos de etate disveloppava sever generalisate urticaria gigante e polyarthralgia le quales subsideva post tres dies de tractamento vigorose.

Tres menses plus tarde le patiente disveloppava scleritis de incognite etiologia, characterisate per un curso tempestuose de 12 menses de duration e per su aggravation progressive in despecto de intense mesuras therapeutic.

Dece-un menses post le declaration del scleritis le patiente se plangeva de intensissime dolores occipital, vertigine, tinnito, e leve grados de surditate. Le symptomas ocular se re-accentuava. Le bulba sinistro-ocular esseva allargate a duo vices su dimensiones normal. Illo esseva tense e hyperesthetic. Le fundo esseva obscurate per diffuse opacitates vitrose. Etiam se declarava sever amblyopia al mesme latere. Fundoscopia del oculo dextere revelava papilledema 4+ con hemorrhagias flammiforme e exsudatos perivascular. Le liquido spinal habeva un pression de plus que 600 mm. Le sedimentation erythrocytic esseva 110 mm per hora.

Bilateral craniectomia subtemporal esseva effectuate. Le matre dur se monstrava marcatemente spissificate in ambe regiones temporal, con un spissitate de inter ¼ e ⅛ pollice. Al superficie exterior illo esseva jalnastre e avascular. A su superficie interior illo esseva plus molle e plus tosto rosicolor. Esseva notate nulle signo de hematoma subdural al un o al altere latere, e le subjacente cerebro pareva esser normal, con le exception que illo se trovava sub un pression augmentate. Le examine

microscopic de specimens bioptic del matre dur revelava indicios de un inflammation allergic. Esseva trovate in le sectiones nulle signo de tuberculose o de non importa qual altere specific processo inflammatori.

Esseva initiate un intense therapia a ACTH e corticosteroides. Intra 24 horas le terribile mal de capite e dolores ocular se meliorava. Intra alicun dies illos deveniva quasi negligibile. Le sedimentation descendeva gradualmente a 5 mm per hora. Le pression del liquido spinal descendeva a 220 mm. Le opacitates vitrose in le oculo sinistre comenciava clarificar se. Intra un mense, un certe grado de vision habeva retornate a ille oculo.

Le patiente deveniva ambulante. Le dosages del steroides esseva reducite. Dece-un menses post le operation le patiente poteva recomenciar su travalio usual a base de tempore quasi complete. Al tempore del redaction del presente reporto, ancora un anno ha passate, e le patiente continua in su empleo.

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HEMORRHAGIC PERICARDIAL FLUID IN ACUTE BENIGN NONSPECIFIC PERICARDITIS: REPORT OF A CASE AND REVIEW OF THE LITERATURE*

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Acute pericarditis of unknown cause and benign course has been described in the American literature for over 100 years.[1] It has been described as occur-

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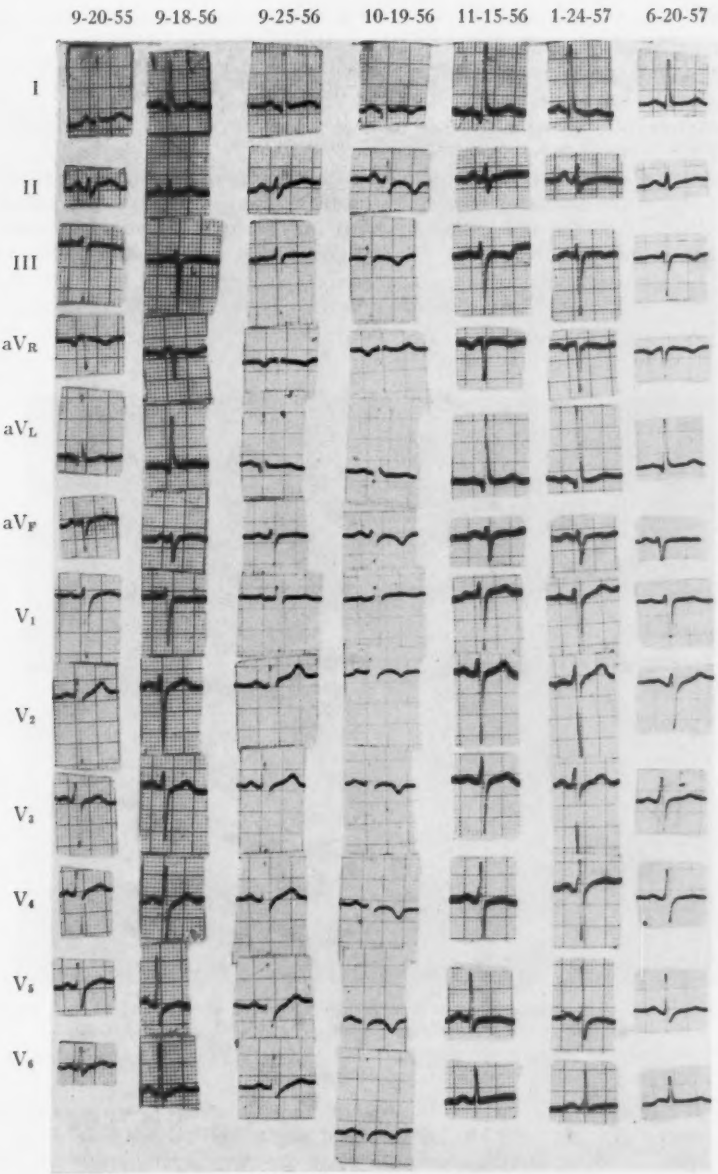


FIG. 1. 9/20/55. Electrocardiogram taken 11 months before onset of pericarditis. Slight ST segment elevation is present in I, aVL. 9/18/56. No significant changes have occurred. 9/25/56. No significant changes have occurred. 10/19/56. T waves have become inverted in Leads I, II, III, aVF, $V_{2, 3, 4, 5, 6}$. 11/15/56. T waves have returned toward normal but are flat in II, $V_{4, 5, 6}$. They are inverted in III and aVF. 1/24/57. T waves remain flat in III, $V_{4, 5, 6}$. 6/20/57. This electrocardiogram now resembles that taken on 9/20/55.

ring under many conditions,[2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12] but most commonly following acute upper respiratory diseases. Many names have been used [1, 12, 13, 14, 15, 16, 17] and many etiologies have been hypothesized.[18, 19, 20, 21, 22, 23] References to this disease were uncommon in the literature until Barnes and Burchell[24] called attention to it in their report of 14 cases in 1942. Many reports and reviews on this subject have appeared since then.[1, 3, 12-16, 18-20, 25-38]

Pericardial effusion is one of the classic features of this disease, but few descriptions of the character of the effusion have been given, probably because the only indications for pericardiocentesis are in the event of cardiac tamponade, which occurs infrequently, and to obtain fluid for diagnostic studies. We considered hemorrhagic pericardial fluid as seen in this case, and as seen previously by one of us (J. R. B.),[36] to be unusual until we began to review the literature on this subject. Our purpose is to report these findings and to add another case with hemorrhagic pericardial fluid.

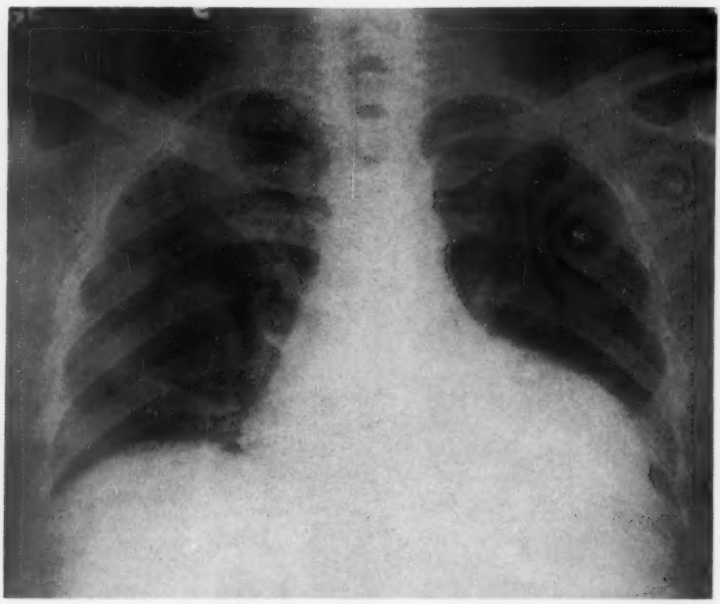


FIG. 2. 9/17/56. The cardiac shadow was greatly increased in size, and at this time the pulsations were markedly decreased, as noted by fluoroscopy.

CASE REPORT

A 38 year old white male haberdasher entered the University of Virginia Hospital on September 17, 1956. He had been in good health until about two and one-half weeks before, when he developed pain, chiefly in the upper anterior chest, though it often radiated to the neck and through to the nuchal region. This pain was constricting in character, sometimes throbbing, and was accentuated by deep breathing and relieved by sitting up. At times it seemed to be worse with exertion and better with rest, but it had been present continuously since onset. Two days prior to ad-

mission the patient's temperature had been 101° F. orally, and he had had heavy sweats for the previous three nights. Systems review, past history and family history were noncontributory.

Physical examination revealed a slightly obese male who was pleasant and cooperative but somewhat apprehensive. His temperature was 100.2° F. orally. The head, ears, eyes, nose and throat were normal, as were the neck and lymph glands. The chest was normal. The heart was thought to be slightly enlarged. A pericardial rub was present at the left sternal border and was heard best in inspiration. The heart rate was 116 per minute and the rhythm was regular. The blood pressure was 110/88 mm. of Hg. A definite paradoxic pulse was present. The abdomen was normal, as was the rest of the physical examination.

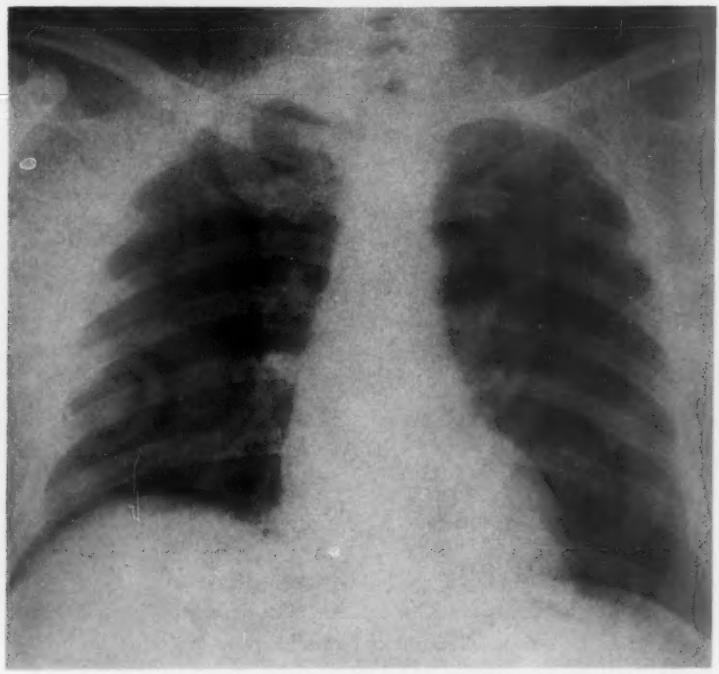


FIG. 3. 9/27/56. The heart had decreased in size, and fluoroscopy at this time revealed increased pulsation.

Laboratory studies revealed a normal urine with a specific gravity of 1.030. The blood urea was 26 mg.%, and the white blood cell count was 8,900 per cubic millimeter, with 69% segmented cells, 20% small lymphocytes, 4% monocytes and 7% eosinophils. The hematocrit was 46%. Platelet count was normal. Bleeding, clotting and prothrombin times were all normal. The sedimentation rate was 21 mm./hr. (Bray). C-reactive protein was 1 plus. Heterophil, brucella and tularemia agglutinations were all negative. L.E. preparations were negative on three occasions. Stool examination was normal. Wassermann and Kahn reactions were negative. The serum cholesterol was 250 mg.% and a two-hour postprandial blood sugar was 106 mg.%. A blood culture was negative.

Hospital Course: After admission the patient's temperature never exceeded 99.6° F. orally. Pain was readily controlled with codeine and Bufferin. Electrocardiograms are shown in figure 1. A chest x-ray showed considerable enlargement of the cardiac shadow, with a cardio-thoracic ratio of .65 (figure 2). Cardiac fluoroscopy revealed a large heart with rounded borders and markedly decreased pulsations. The venous pressure was 170 mm. of water. On September 19, 1956, a diagnostic pericardiocentesis was done and about 150 c.c. of very bloody fluid which did not clot were removed. Cell block of this fluid revealed many red blood cells and a few white blood cells, but no tumor cells. Smears and cultures were negative for

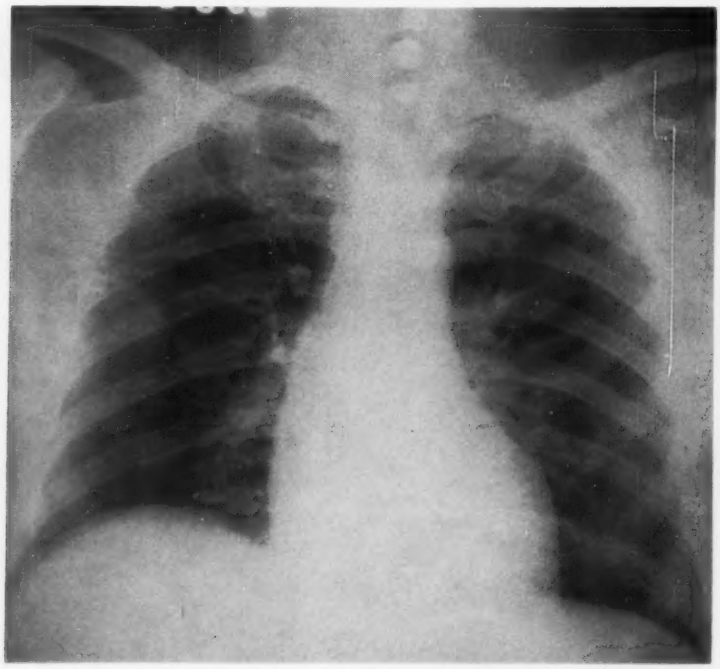


FIG. 4. 9/19/56. This shows further decrease in cardiac size.

pyogenic bacteria, acid-fast bacilli or fungi. The venous pressure was 120 mm. of water following the tap. Fluoroscopy following pericardial tap showed decrease in size of the cardiac shadow and increase in the amplitude of the pulsations (figure 3). The patient's course was uncomplicated and he was discharged from the hospital on October 1, 1956.

On several follow-up visits he has been asymptomatic. Chest films indicate that the heart size has become normal and remained so (figures 4 and 5). On October 19, 1956, T-waves were inverted in Leads I, II, III, aVF and V_2–V_6. Nine months after the initial episode the patient is in excellent health, and the electrocardiogram is now normal and resembles one taken 11 months before the pericarditis developed.

We have been able to find reports of 22 cases, including our own, in which pericardial taps were done.[3, 13, 20, 36, 37, 38, 39] This information is summarized

in table 1. Of these 22 cases, one was a dry tap [37] and a second was described as blood-tinged but thought to be due to a previous traumatic tap.[13] Of the remaining 20, 14 were hemorrhagic, varying from a few red blood cells up to very bloody, with a hematocrit of 10% in one and 6% in two others.

Several authors have commented upon the hemorrhagic nature of the pericardial fluid, but only recently has some emphasis been placed on this point by Reid et al.[20, 39] They conclude that effusions during the first 10 to 14 days of illness are usually serous, but the fluid obtained later in the course of the disease

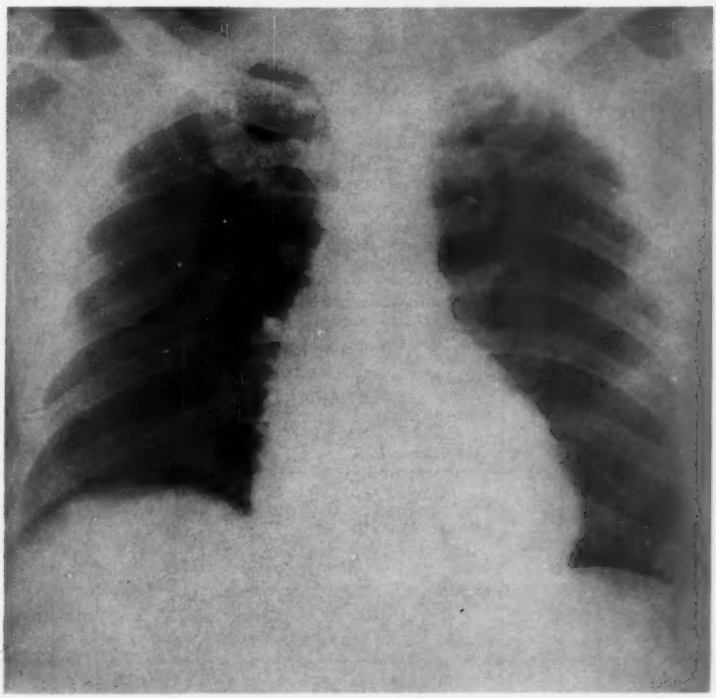


FIG. 5. 1/24/57. The cardiac contour is now normal, and subsequent x-rays show no further change.

is serosanguineous. Our findings have tended to agree with this, but we have found two cases reported as serosanguineous before the tenth day, one on the fourth day,[41] and the other on the fifth day [36] of illness, and a third case described as serosanguineous on the eleventh day.[38] The few reports given, with still fewer details as to the day of illness when the tap was done, do not allow us to draw a more definite conclusion on this point.

Several fatalities said to be due to this disease have appeared in the literature, and some of these have demonstrated bloody pericardial effusion at autopsy.[39, 42, 43, 44, 45] One of these deaths [43] occurred after anticoagulant therapy for what was thought to be an infarction; the cause of death was cardiac tamponade with hemorrhagic pericardial fluid.

TABLE 1
22 Patients Reported to Have Had Pericardial Taps

Authors	No. of Patients	Character of Fluid	Amount	Day of Illness When Tapped
Nathan and Dathe[3]	5	Reddish amber fluid Hemorrhagic (Hct. 10%) Hemorrhagic (Hct. 6%) Clear amber Hemorrhagic (tapped 2 times)	350 c.c. 50 c.c. 175 c.c. 10 c.c. 3 c.c. 40 c.c.	50 17 16 5 15 16
Sease and Beckwith[36]	2	Serosanguineous Cloud yellow	200 c.c. 10 c.c.	5 12
Camp and Clark[37]	2	Bloody (tapped 2 times) Dry tap	? 10 c.c. –0–	25 27 1
Porter, Clark and Porter[38]	4	Serohemorrhagic Serosanguineous Serohemorrhagic Serohemorrhagic	160 c.c. 110 c.c. 90 c.c. Not stated	27 11 Not stated Not stated
Levy and Patterson[13]	3	Blood-tinged (thought to be traumatic) Straw-colored Straw-colored	120 c.c. 10 c.c. Not stated	5 Not stated Not stated
Taubenhaus and Brams[40]	1	Amber colored (tapped 4 times, some RBC and WBC)	50–100 c.c.	Not stated
Reid, Hutchinson and Price[20,39]	3	Straw-colored Straw-colored (tapped 2 times) Bloody (tapped 2 times)	100 c.c. 150 c.c. 50 c.c. 410 c.c. 550 c.c. (1,000 c.c. at autopsy)	10 5 12 30 36
Rakov[41]	1	Serosanguineous (occ. RBC)	50 c.c.	4
Present case	1	Very bloody	150 c.c.	20

The realization that hemorrhage into the pericardium does occur in acute benign nonspecific pericarditis seems to have at least two very practical applications: (1) anticoagulants are contraindicated in this disease, which is often mistakenly diagnosed as myocardial infarction, and (2) bloody pericardial fluid does not necessarily mean more serious disease, such as tuberculous pericarditis or even effusion due to malignant neoplasm.

ADDENDUM

Since the writing of this paper, another report of a case of cardiac tamponade due to hemopericardium in acute nonspecific pericarditis has appeared in the

literature (Goodman, H. L.: Acute nonspecific pericarditis with cardiac tamponade: a fatal case associated with anticoagulant therapy, Ann. Int. Med. 48: 406, 1958). This was a 76 year old Negro female who had received Dicumarol for 14 days prior to her death with a mistaken diagnosis of myocardial infarction. This author points out again that anticoagulants are contraindicated in acute nonspecific pericarditis.

Summario in Interlingua

Descriptiones de pericarditis acute de causa incognoscite e de curso benigne existe depost multe annos. Sed ben que effusion pericardial es un del aspectos classic del morbo, pauc descriptiones presta attention al character del effusion. Le constatation de liquido hemorrhagic in un patiente con acute pericarditis benigne inspirava un revista del thema.

Le patiente esseva un masculo de racia blanc de 38 annos de etate qui disveloppava dolores thoracic, de character pleuritic, due septimanas e medie ante su admission al hospital. Elevation del temperatura e sudor nocturne esseva associate. Le examine physic revelava un fricamento pericardial, allargamento cardiac, e pulso paradoxe. Le studios laboratorial esseva omnes normal, con le exception de un accelerate sedimentation. Le roentgenoscopia del thorace revelava allargamento cardiac, e le fluoroscopia monstrava un marcate reduction del pulsationes. Esseva effectuate puncturation pericardial, e 150 cm^3 de liquido sanguinose esseva extrahite. Culturas, frottis, e bloco cellular monstrava nulle bacterios, fungos, o cellulas tumoral.

Le patiente se meliorava clinicamente. Le dimensiones de su corde retornava a valores normal, e ille se trova ben novem menses post su dimission ab le hospital. Electrocardiogrammas, habente exhibite alterationes compatibile con pericarditis, redeveniva normal.

Un revista del litteratura resultava in un lista de 22 casos in que puncturation pericardial esseva effectuate. In 14 del 22, le liquido esseva hemorrhagic.

Al minus duo patientes ha morite ab tamponage cardiac causate per pericarditis hemorrhagic post administrationes de anticoagulantes, e il pare que therapia anticoagulante es contraindicate in pericarditis benigne acute. Per consequentia il es importante differentiar inter iste condition e acute infarcimento myocardial.

Le constatation de un hemorrhagic effusion pericardial non indica necessarimente un serie morbo, tal como tuberculose o tumor.

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FATAL "WATERHOUSE-FRIDERICHSEN SYNDROME" DUE TO DICUMAROL*

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Bilateral adrenal hemorrhage incident to anticoagulant therapy is a rare occurrence. Only four cases have been documented in the literature since 1952. Three of these patients had received heparin, and one patient had been maintained on Dicumarol prior to death.[1, 2, 3] In the Dicumarol-treated patient, emboli and infarctions were discovered in various organs; therefore, adrenal infarction could not be taken conclusively as the primary cause of the hemorrhage.[3] Our case is presented because of the definite association of adrenal hemorrhage with anticoagulant therapy and the absence of any embolic phenomena at the postmortem examination.

Case Report

A 69 year old white woman was admitted to the Cincinnati Jewish Hospital on March 12, 1958, complaining of severe chest pain radiating to the back and left arm of several hours' duration. For 10 years prior to admission she had experienced symptoms typical of angina pectoris, which had become more severe two weeks before hospitalization. A history of recently discovered diabetes mellitus was also obtained from the patient.

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Physical examination on admission revealed a blood pressure of 180/90 mm. Hg, a pulse rate of 94 per minute, and a temperature of 99° F. rectally. The cardiac rhythm was regular and the heart sounds were of fair quality. Initial laboratory work showed: red blood cell count, 4,800,000 per cubic millimeter; total leukocyte count, 21,300 per cubic millimeter, with 90% neutrophils; blood sugar, 623 mg.%; blood urea nitrogen, 32 mg.%; serum transaminase, 102 units. There were marked changes in the electrocardiographic pattern, compatible with the diagnosis of an acute posterior myocardial infarction.

Heparin sodium was administered shortly after admission in a dose of 50 mg. intravenously every four hours. At the same time, 300 mg. of Dicumarol were given orally. The initial prothrombin time was 15 seconds or 60% of the control value. The patient's diabetic state was easily controlled with small doses of regular insulin,

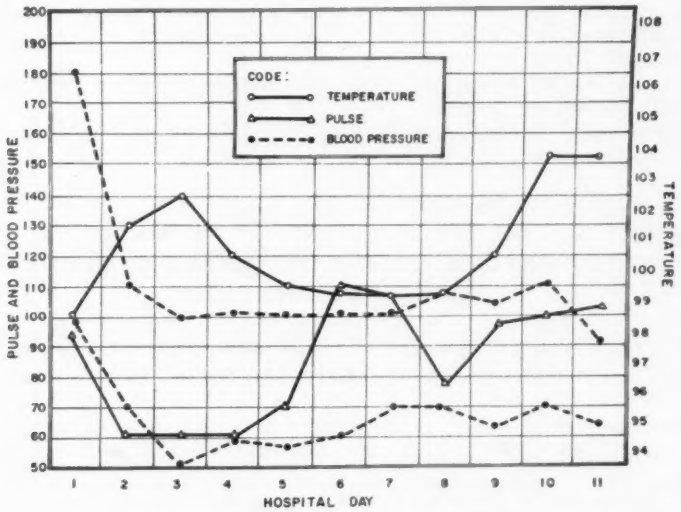


FIG. 1. Vital signs during hospital course.

and presented no problem during the remainder of her hospital course. Her subsequent hospital course is presented in graphic form (figure 1 and table 1), showing the vital signs and pertinent laboratory data. As shown in figure 1, her temperature was elevated the first four days of hospitalization, and returned to normal levels between the sixth and the eighth day.

During the first three days the patient had recurrent episodes of chest pain, her pulse rate dropped to 60 per minute, and her blood pressure decreased to 96/60 mm. Hg, without evidence of pulsus paradoxus. A faint pericardial friction rub and a soft apical systolic murmur were heard. The electrocardiogram revealed a complete atrioventricular dissociation. A low serum sodium and chloride were discovered on the third hospital day. The exact cause of these values was not entirely clear, and will be considered in the discussion.

In the following three-day period the patient's general clinical condition seemed to improve. Her temperature returned to normal, and she resumed a regular sinus rhythm at the rate of 110 per minute. During this time, however, there was a precipitous drop of the prothrombin time to 45 seconds or 10% of the control value,

despite the fact that she had received a total of only 500 mg. of Dicumarol. Dicumarol was immediately discontinued, and oral Mephyton therapy was started. In spite of antidotal therapy, the prothrombin time remained at toxic levels for the next four days. At this time microscopic hematuria was discovered. Simultaneously with these events, the clinical status of the patient began to deteriorate. She developed a nonbloody diarrhea which was subsequently shown to be free of bacterial pathogens. Severe dehydration was observed despite what seemed to be adequate intravenous fluid and electrolyte therapy during the preceding hospital period. Her urinary output, which had ranged from 700 c.c. to 1,600 c.c. per day, diminished to 300 c.c. per day.

The final phase of her clinical course was characterized by a rise in body temperature, an increase in the severity of her diarrhea, and progressive lethargy. Her heart sounds became distant and she developed moderate abdominal distention. In view of the persistent low serum sodium and chloride, 250 c.c. of hypertonic saline were ad-

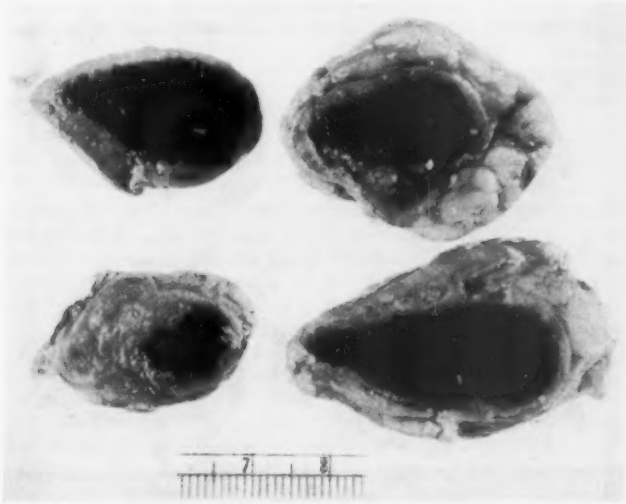


FIG. 2. Sectioned adrenal glands.

ministered. This resulted in a temporary reversal of her lethargic state and a moderate increase in her 24-hour urinary output.

On the patient's eleventh and final hospital day, her terminal status was apparent in marked dehydration, a drop in the blood pressure to 90/65 mm. Hg, and almost complete unresponsiveness. The heart sounds were muffled. Physical signs of pneumonic consolidation were elicited over the left lower lobe posteriorly. A portable chest x-ray, however, was interpreted as showing probable cardiac enlargement, pulmonary congestion, and moderate bilateral pleural effusion. The serum sodium remained low, at 125 mEq./L. The prothrombin time was 20 seconds, or 30% of the control value. Microscopic hematuria was again noted. The patient lapsed into a semicomatose state and died within a few hours.

Necropsy Report: Postmortem examination was performed two hours after death. There was no evidence of petechiae or purpura externally. Approximately 400 c.c. of clear yellow fluid were found on opening the abdomen. The peritoneal surface was smooth and glistening. Clear yellow fluid was discovered in each pleural cavity,

measuring 500 c.c. in the right and 2,000 c.c. in the left. The pericardial cavity yielded 200 c.c. of dark red, unclotted blood.

The heart was dilated and weighed 510 gm. The pericardium was roughened. The left coronary artery was very calcific, and contained an old thrombus which had partially recanalized. There was a considerable amount of fibrosis at the site of the interventricular septum. There was a recent occlusion of the right coronary artery, with a large area of myomalacia in the left ventricle. In addition, there was an extensive ecchymotic area located in the posterior wall of the right and left ventricle. There were no mural thrombi.

TABLE 1

Summary of Laboratory Values

Hospital Day.....	1	2	3	4	5	6	7	8	9	10	11
Prothrombin time %	60	70	21	17	10	—	10	13	33	45	38
Seconds	15	17	28	32	45	—	45	37	21	18	20
Hemoglobin gm.%	14.4	—	—	—	—	—	—	12.4	—	11.1	—
Blood urea nitrogen mg.%	32	42	37	35	—	22	—	—	—	11	—
Serum sodium mEq./L.	—	—	126	—	—	—	124	—	—	121	125
Serum potassium mEq./L.	—	—	4.3	—	—	—	4.3	—	—	4.3	4.3
White blood cell count No./cu.mm.	21,000	30,800	25,800	14,250	19,900	—	23,000	15,400	—	26,000	—
Neutrophils	96	82	91	91	94	—	80	95	—	80	—
Lymphocytes	4	13	9	8	6	—	11	2	—	14	—

The lungs were of normal size and weight. Congestion was present bilaterally in the lower lobes. Consolidation was not evident. Microscopic examination revealed acute passive congestion, with no active inflammation. The spleen, liver, pancreas and kidneys were not remarkable on gross examination, and microscopically revealed only passive congestion. The brain was grossly normal, without any evidence of hemorrhage, thrombosis or inflammation.

There were no gross abnormalities in the alimentary tract. Sections of the small intestine revealed a diffuse, active inflammatory reaction in the mucosa and submucosa. The inflammatory cells were chiefly of the large mononuclear type, but included an appreciable number of polymorphonuclear leukocytes.

The adrenal glands showed the most remarkable abnormality. They were tremendously enlarged, measuring 5 by 4 cm. in their broadest diameters (figure 2). Both cortices were replaced by massive areas of hemorrhage. Microscopic sections revealed almost complete obliteration of the architecture of both adrenal glands by this hemorrhage, and only a shadowy residue of the cortical structure was visible. Thrombi were not found in the adrenal arteries or veins. A blood culture obtained intracardially two hours post mortem was sterile.

DISCUSSION

Merz and Aufdermaur reported the first two examples of this syndrome in 1952.[1] In both of these patients heparin was the anticoagulant used. The clinical course of both patients was strikingly similar, and was manifested by sudden peripheral vascular collapse resulting in death within several days. Adrenal insufficiency was not recognized clinically. Review of the postmortem findings in both cases revealed bilateral adrenal hemorrhage, without any evidence of thrombi in the adrenal vessels. In one of the cases there was evidence of a generalized hemorrhagic diathesis. In 1956 Thorn et al.[2] presented an interesting account of a patient who developed signs of acute adrenal insufficiency during the course of heparin therapy. This patient was treated vigorously with

steroid compounds and survived. Subsequent detailed endocrine studies demonstrated unequivocal signs of chronic adrenal insufficiency.

The most recent report of adrenal hemorrhage complicating anticoagulant therapy was presented by Chokas.[3] This patient had been on Dicumarol therapy for a recent coronary occlusion. Four days prior to his death he developed hyperpyrexia, disorientation, a fall in blood pressure, and abdominal pain. Terminally he became cyanotic and developed irreversible shock. At no time during the course of his therapy was the prothrombin time prolonged beyond the therapeutic range. Autopsy revealed evidence of a generalized hemorrhagic diathesis involving multiple organs. There was a large recent infarct of the posterolateral wall of the left ventricular myocardium, with an organizing mural thrombus in the left ventricle. Bilateral massive hemorrhagic infarction of the adrenal glands was present, with thrombi in the main adrenal veins. Areas of recent infarction in both kidneys and the spleen were found. Because of these multiple infarcts, the author stated that it was not definitely possible to exclude embolization to both adrenals as the cause of the hemorrhage. He therefore could not assert unequivocally that Dicumarol was the etiologic agent.

Adrenal hemorrhage may be caused by the following conditions:

1. Destruction of gland substance by tumor or infection.
2. Adrenal capillary injury which may occur with convulsions, trauma and emboli.
3. Generalized hemorrhagic states, including hypoprothrombinemia and other blood dyscrasias.
4. Thrombosis of the adrenal vein with infarction.
5. Idiopathic or spontaneous adrenal hemorrhage.

Of these, probably the most common is septicemia or overwhelming infection. This is usually observed with meningococcemia, but may occur with septicemia due to staphylococcus, pneumococcus, streptococcus or *Hemophilus influenzae*. Generalized hemorrhagic manifestations are almost always present, and the onset is rapidly followed by cyanosis and petechial rash. Spontaneous adrenal hemorrhage has shown an increasing incidence in the last two decades.[4] It may occur at any age, and with equal frequency in both sexes. Abdominal pain, usually localized to the epigastric region, is a very frequent finding, and is often associated with tenderness and muscle spasm. Later, pallor, prostration, fall in blood pressure, nausea, vomiting, cyanosis and finally shock ensue. Fever and leukocytosis are often present. In contrast to adrenal hemorrhage of infectious origin, purpura is usually absent, and the symptoms of adrenal insufficiency develop more slowly.

The present case is illustrative of spontaneous adrenal hemorrhage caused by Dicumarol-induced hypoprothrombinemia, and is the first clearly defined example of this unusual event reported to date. The patient displayed a marked idiosyncrasy to Dicumarol. A mere 550 mg., administered over a three-day period, lowered the prothrombin time to 10% of the control value (or 45 seconds) on the fifth day. Several reasons could be postulated to explain this phenomenon.[5] There is a marked individual variation in the response to the effects of Dicumarol which is dependent upon the difference in absorption and in the rate of catabolism of the drug. This is probably the most important factor in determination of Dicumarol idiosyncrasy. An individual patient may

excrete anywhere from 0 to 36% of the drug in the feces with a given dose. Likewise, on the same dose one patient may maintain measurable levels for more than nine days, whereas in another the level may become negligible in 48 hours. Salicylates produce a lowering of the prothrombin level, and a synergistic effect may be noted in patients on Dicumarol therapy. Oral antibiotics, particularly the broad-spectrum variety, may cause a decrease in the production of vitamin K by the elimination of intestinal bacteria. Renal insufficiency may be a significant factor by interfering with the excretion of the drug. For some undetermined reasons, fever may enhance the action of the drug and make the patient more susceptible to its pharmacologic action. The majority of the serious hemorrhagic complications may be expected when the prothrombin time is in excess of 40 seconds, and this level should be avoided if at all possible.[5]

Our patient had excessive hypoprothrombinemia for three days, in the range of 10% of the control values (or 45 seconds). As evidence of this excessive anticoagulant effect, microscopic hematuria was noted on her seventh and eleventh hospital days.

Nevertheless, there was no postmortem evidence of a generalized hemorrhagic diathesis. There were no mural thrombi, and no signs of infarction in any organ. It is especially important to note that no thrombi were found in any of the adrenal vessels. The only evidence of infection was present in the mucosa of the small intestine, but all cultures were negative, which would tend to exclude a septicemic process. Thus none of the factors known to produce or to predispose to the occurrence of adrenal hemorrhage could be found in this case, with the exception of the drug-induced hypoprothrombinemia.

It is difficult to state with accuracy the time of onset of the adrenal hemorrhage in this patient. However, the diarrhea began on the sixth hospital day and was followed in quick succession by dehydration, fever, lethargy and abdominal distention. There was a fall in the hemoglobin and red cell count, together with an increasing leukocytosis during this interval.

As previously mentioned, the low serum sodium and chloride on the third hospital day were unusual and unexpected findings. The patient at this time had an adequate urinary output, although the blood urea nitrogen was elevated to 37 mg.%. During her first few hospital days she had been maintained on salt-free fluids. Conceivably, this bizarre electrolyte pattern might have been due to a combination of true salt depletion and dehydration secondary to an uncontrolled diabetic state prior to admission. Undoubtedly this condition was aggravated by treatment with the salt-free solutions after admission to the hospital.

Persistence of the low serum sodium, decreased urinary output, hypotension and lethargy in the last three days of the patient's life seemed to substantiate clearly the progressive development of adrenal insufficiency. The day prior to her death, the patient made a brief but dramatic response to the infusion of hypertonic saline. The significance of this response was not fully appreciated, and this therapy was not pursued vigorously.

Summary

This case is presented as a well defined example of the unusual complication of bilateral adrenal hemorrhage in the course of anticoagulant therapy. The

various causes of adrenal hemorrhage are reviewed and discussed. The possible reasons for Dicumarol idiosyncrasy are considered. It is hoped that this report may alert others to this rare syndrome and thus encourage earlier recognition and treatment.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Dr. Philip Wasserman, Director of Clinical Laboratories, Jewish Hospital, who performed the gross and microscopic postmortem examination on this patient.

SUMMARIO IN INTERLINGUA

Es presentate un caso de hemorrhagia adrenal bilateral, associate con therapia anticoagulante in un patiente con infarcimento myocardial. Es revistate e analysate le quatro previe reportos de casos concernite con iste thema. Solmente un altere patiente habeva essite tractate con Dicumarol, e su caso esseva complicate per embolisation con multiple areas de infarcimento in varie organos. Le presente caso monstrava un definite association inter le hemorrhagia adrenal e le therapia anticoagulante. In plus, nulle phenomenos embolic esseva incontrate in le examine post morte.

Le patiente esseva un femina de racia blanc de 69 annos de etate qui habeva essite admittite al Hospital Judee Cincinnati a causa de acute infarcimento postero-myocardial. Post solmente 500 mg de Dicumarol administrate in le curso de un periodo de cinque dies, le tempore de prothrombina descendeva a 10%, i.e., illo amontava a 45 secundas. Iste nivello persisteva durante quatro dies in despecto de therapia antidotal con Mephytona oral. Duo dies ante su morte, le patiente disveloppava signos de un progressive insufficientia adrenal. Le plus frappante constatation durante le examine necroptic concerneva le glandulas adrenal. Illos esseva enormemente allargate, mesurante 5 per 4 cm in lor diametros maximal, con le cortices a ambe lateres reimplaciate per massive areas de hemorrhagia. Microsectiones revelava le quasi complete oblitteration del architectura in ambe glandulas adrenal in consequentia de iste hemorrhagia, e solmente un vage residuo del structura cortical habeva remanite visibile.

Es revistate e discutite le varie causas de hemorrhagia adrenal. Es considerate le rationes possibile pro le occurrentia de susceptibilitate idiosyncratic a Dicumarol. Es exprimite le spero que le presente reporto va servir a alertar alteres con respecto a iste infrequente syndrome e assi a incoragiar le plus precoce recognition e le plus prompte tractamento de illo.

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EDITORIAL

AUTO-IMMUNIZATION AND AUTO-ANTIBODIES

THE capacity of the animal body to react to the presence of micro-organisms or other foreign organic material as a protective measure has been well known for over half a century. Much has been learned regarding the mechanisms by which this is accomplished and the circulating antibodies which participate in providing this immunity. Under natural conditions these reactions are nearly always beneficial if they are efficient, and the term immunity has come to indicate a favorable and highly desirable state. The introduction into the body of blood or tissue products of another individual of the same species will often stimulate a similar reaction which may be less obviously beneficial. There are genetic differences between individuals of the same species, so that such material acts like foreign tissue, it stimulates the formation of iso-antibodies and is eliminated.

Except for a few highly specialized tissues, in the past it had usually been very difficult or impossible experimentally to stimulate the formation of "auto-antibodies" by the injection into a subject of preparations from his own unaltered tissues, and the possibility of "auto-immunization" was largely dismissed. During the last two decades, however, clinical and experimental evidence for the occurrence of such "auto-immunizations" has been accumulating, and the question of their clinical and pathologic significance has become extremely important.

The first recognized and most convincing instances of such antibodies are the autohemolysins which appear in the blood in cases of acquired hemolytic anemia. First brought to notice by Widal, Chauffard and their associates 50 years ago, but then largely forgotten, they were rediscovered and adequately characterized as antibodies by Dameshek and his associates.[1] These substances differ in some important details from the usual hetero-antibodies; they are more elusive, they are as a rule "incomplete," or "coating," or "blocking" antibodies, and like the Rh antibodies require special methods for their detection. The most practicable procedure is the use of Coombs' serum, obtained from a rabbit "immunized" with human globulin. If auto-antibody, which is usually a gamma globulin, is present in the patient's serum, it will adhere tightly and coat the surface of the red cells of the patient, which then become agglutinable in the Coombs' anti-human-globulin serum.

This field has been studied intensively, and there can be little doubt that these substances are true antibodies. In electrophoretic tests they are found

[1] Dameshek, W., and Schwartz, S. O.: Hemolysins as the cause of clinical and experimental hemolytic anemias with particular reference to the nature of spherocytosis and increased fragility, Am. J. M. Sc. **196**: 759, 1938.

in the globulin fraction and usually with the gamma globulins. They resemble the usual antibodies in their degree of resistance to heat. As a rule they have a similar degree of specificity, under suitable conditions they can be eluted and they may then be reabsorbed by other cells. Evidence that these antibodies injure the red cells and cause the anemia is strong. Although there are some discrepancies not yet well explained, this view as to their pathogenic significance has won fairly general acceptance.

It seems highly probable that a similar mechanism with a different antibody is responsible for destroying the platelets in many cases of idiopathic thrombocytopenic purpura. This is possibly true also for some cases of severe granulocytopenia, although there is little if any convincing direct evidence of auto-antibodies in the latter.

The mechanism by which auto-antibody production is stimulated in these patients is not clear. In animal experiments it is helpful and may be essential to cause some injury or chemical alteration of the cells in order to induce formation of auto-antibodies. A common device has been to add some sort of adjuvant to the cells or tissue to be injected. These often include killed bacteria or bacterial products, such as hemolytic streptococci, mycobacteria, or bacterial polysaccharides, which may combine with the tissue substances to form a haptine. Some inert oils are often included to slow down and protract absorption, producing persistent areas of productive inflammation in the tissues. It seems likely that some similar injury to cells or tissue occurs in man to initiate this continuing, self-propagating reaction, but any discussion as to the details of such a process would be purely speculative.

Blood cells are readily accessible and available for experimentation. The study of analogous reactions involving fixed tissues is much more difficult. The most direct proof of the action of auto-antibodies on tissue cells has been obtained in certain cases of chronic thyroiditis, particularly of the Hashimoto (lymphadenoid) type.[2, 3] Witebsky et al.[4] showed that the injection of homologous thyroid extract (with adjuvants) into rabbits resulted in the appearance in the serum of iso-antibodies to thyroid. These were demonstrated most readily by agglutination tests, using red cells which were first exposed to dilute tannic acid and then immersed in an extract of rabbit thyroid before the test. The "tanned" cells readily became coated with protein from the thyroid extract and they were agglutinated if there was antibody in the serum of the treated rabbit. The reaction was specific —negative reactions were obtained with normal sera and with extracts of organs other than the thyroid. Complement fixation and precipitin reactions were obtained but were weaker. It was clearly shown that thyroglobulin was the protein concerned in this reaction.

[2] Witebsky, E., and Rose, N. R.: Studies on organ specificity. IV. Production of rabbit thyroid antibodies in rabbit, J. Immunol. **76**: 408–416 (June) 1956.

[3] Roit, I. M., Doniach, D., Campbell, P. N., and Hudson, R. V.: Autoantibodies in Hashimoto's disease (lymphadenoid goitre), Lancet **2**: 820–821, 1956.

[4] Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R., and Egan, R. W.: Chronic thyroiditis and autoimmunization, J. A. M. A. **164**: 1439–1447 (July 27) 1957.

Auto-antibodies were also induced by injecting a rabbit with thyroglobulin or an extract made from one excised lobe of its own thyroid.[5] After an interval its serum gave positive reactions with an extract of its own gland, and the remaining lobe showed injury ("chronic thyroiditis") from the injections.

These authors [4] also obtained positive reactions with extracts of human thyroid and serum from human subjects in 12 cases, all showing "chronic thyroiditis," sometimes in high dilution. Some other cases clinically similar gave negative reactions, as did patients with other types of thyroid disease. The specificity of the reaction was confirmed by showing that it could be inhibited by adding extract from a normal human thyroid or a colloid goiter to the serum an hour before the test was carried out, but not by extracts of other organs.

Witebsky points out that these observations do not prove that the circulating auto-antibodies directly cause the injury to the thyroid. This presumably is brought about by antibody fixed to the cells, like "coating" antibody, which can not be demonstrated satisfactorily by present technical methods. Furthermore the demonstration of antibody may be hampered or prevented by its usual tendency to become fixed to the corresponding antigen, in the thyroid, and what is circulating may be merely a transient and insignificant excess.

These observations receive confirmation in the report of Roit et al.[3] who observed positive flocculation tests with the serum of six cases of Hashimoto's disease, using both extracts of normal human thyroid glands and purified human thyroglobulin, but not with extracts of other organs. They also believe that the patients are "immunized" to their own thyroglobulin and that the thyroid is damaged by the action of these auto-antibodies on the thyroglobulin in their own gland. A protein which is similar to if not identical with thyroglobulin has been reported in the blood of such cases, but neither group could demonstrate the underlying etiological factor which permitted the thyroglobulin to escape from the thyroid into the general circulation, where it acts like a foreign protein.

Witebsky points out that the major criteria necessary to prove the pathogenic significance of an auto-antibody have been fairly well met in this instance. Circulating antibodies have been demonstrated, active at body temperature; the specific antigen has been identified, similar antibodies have been produced in experimental animals, and pathologic lesions have been produced which basically resemble those in the human disease.

Other diseases in which auto-antibodies have been reported or strongly suspected are mainly included among the collagen diseases. In such conditions the major injury is to tissue cells, and the demonstration of antibody fixed to such cells is technically difficult and largely impracticable at

[5] Rose, N. R., and Witebsky, E.: Studies on organ specificity. V. Changes in thyroid glands of rabbits following active immunization with rabbit thyroid extracts, J. Immunol. 76: 417–427 (June) 1956.

present. Many attempts have been made to demonstrate circulating antibody, using extracts of normal organs. Precipitin tests and quantitative complement fixation tests are commonly used, and also agglutination tests with inert particles (collodion, bentonite, "tanned" or trypsinized red cells), which have been coated with the antigen in question. New, more sensitive technics have been devised, but elaborate controls are necessary and there is often much overlapping and lack of specificity as to organ and even as to species. Some confirmation is obtained if the antibody can be removed or inactivated with the specific antigen and not with a suitable control preparation.

In acute rheumatic fever some suggestive evidence has been reported. For example, Gear [6] produced a hetero-antiserum by injecting rabbits with cardiac endothelium of guinea pigs, which on intrapericardial injection into normal guinea pigs produced pericarditis together with lesions resembling those of acute rheumatic fever "in sections of the heart." In six of 12 cases of this disease he found antibodies (precipitins in low titer) to an extract of normal human heart. Cavelti (1945) had demonstrated similar antiheart antibodies by agglutination of coated collodion particles.

Stronger evidence of auto-antibodies has been advanced in the case of rheumatoid arthritis. For many years it has been known that the serum in this disease contains a peculiar agglutinin commonly known as the "rheumatoid factor." This was demonstrated among others by Cecil (1931) with streptococci, which he suspected to be the cause of this disease. It was soon found that other bacteria would serve as well and, that the factor could be detected and measured by the agglutination of sheep red blood cells which had been feebly sensitized with a rabbit antisheep serum but not to the point of causing visible agglutination. Human cells or those of other species can be used if they have been coated with globulin in some way, or if they have been "tanned" or trypsinized so that they will nonspecifically bind protein from the serum. This factor has been intensively studied, but its exact nature and significance are still unsettled.[7] It is a heavy protein, a constituent of the gamma globulin fraction which is commonly increased in rheumatoid arthritis and other collagen diseases. It acts on the globulin coating the red cells or bacteria, not on the actual constituents of the cells. It can combine with some other fractions of gamma globulin to form a precipitate which removes the factor from the serum. It has been shown that the fibrinoid present in the specific lesions contains both fibrin and gamma globulin, and it has been suggested that the rheumatoid factor brings about this precipitation and thus causes or contributes to the formation of the fundamental pathologic lesions in the connective tissue. It has been shown by the use of fluorescent dyes that globulin in the serum

[6] Gear, J.: Autoantibodies and the hyperreactive state in the pathogenesis of disease, Acta med. scandinav. **152**, Supp. **306**: 39–55, 1955.

[7] Vaughan, J. H.: Serum responses in rheumatoid arthritis, Am. J. Med. **26**: 596–613 (Apr.) 1959. (Good review.)

of rheumatoid arthritis also combines with nuclear material in fixed tissue cells.

There is evidence that the rheumatoid factors from different patients vary in composition. They may differ in the way they react with gamma globulins from different normal subjects, being in varying degree precipitated and inactivated by them, or with them, acting as an antigammaglobulin. The factor is not specific for rheumatoid arthritis, being reported positive in about 20% of cases clinically diagnosed as disseminated lupus and occasionally in scleroderma, sarcoid, syphilis, and hepatic diseases. Moreover in 20% to 30% of patients with rheumatoid arthritis, the factor can not be detected, although they have the usual high quota of globulins in the serum. Furthermore it has been shown by Good et al.[8] and by Janeway et al.[9] that clinically typical rheumatoid arthritis occurs in cases both of congenital and acquired agammaglobulinemia and that the disease is actually more frequent (33%) in such subjects than in the general population.

Large amounts of serum from cases of rheumatoid arthritis rich in this factor have been injected into normal volunteers and into subjects with rheumatoid arthritis in a relatively quiescent stage without causing any disturbance whatsoever.

Caution is therefore indicated in assessing the etiologic importance of rheumatoid factor since it is evidently not essential for the initiation or perpetuation of the disease. This all suggests that the factor is probably a secondary or adaptive response to some more fundamental disturbance rather than directly injurious in itself.

Positive serologic reactions have been reported between sera from rheumatoid arthritis and extracts of various human organs. Thus Gajdusek[10, 11] obtained positive complement fixation reactions in low titer in three of six cases using a kidney extract but not with a liver extract. Considerable work along these lines has been reported in Germany, some like Vorlaender,[12] confirming the American observations.

Evidence has also been advanced incriminating auto-antibodies as a factor in causing glomerular nephritis and some cases of the nephrotic syndrome. Among others, Smadel[13] obtained a hetero-nephrotoxic serum in rabbits by injecting material from rat kidneys, which serum caused nephritis on in-

[8] Good, R. A.: Rheumatoid arthritis and agammaglobulinemia, Bull. Rheumat. Dis. **10**: 203–206 (Jan.) 1960.

[9] Janeway, C. A., Gitlin, D., Craig, J. M., and Grice, D. S.: "Collagen disease" in patients with congenital agammaglobulinemia, Tr. A. Am. Physicians **69**: 93–97, 1956.

[10] Gajdusek, D. C.: An "autoimmune" reaction against human tissue antigens in certain acute and chronic diseases. I. Serological investigations, Arch. Int. Med. **101**: 9–29 (Jan.) 1958.

[11] Mackay, I. R., and Gajdusek, D. C.: An "autoimmune" reaction against human tissue antigens in certain acute and chronic diseases. II. Clinical correlations, Arch. Int. Med. **101**: 30–46 (Jan.) 1958.

[12] Vorlaender, K. O.: Weitere Untersuchungen zur Frage der klinischen Bedeutung von Antikörpernachweisen beim Rheumatismus und entzündlichen Erkrankungen, Ztschr. f. d. ges. exper. Med. **120**: 9–22, 1952.

[13] Smadel, J.: Experimental nephritis in rats induced by injection of antikidney serum: preparation and immunological studies of nephrotoxin, J. Exper. Med. **64**: 921–942, 1936.

jection into rats. Schmidt,[14] who has reviewed some of the German work, has pointed out that the nephritis may not arise from a direct action of such toxic sera on the renal tissue. If, for example, a rabbit kidney extract is injected into geese, antibodies to the rabbit renal cells are developed. If this goose anti-rabbit-kidney antiserum is injected into a rabbit, it can be shown by use of fluorescent antibody or proper labeling with radioactive isotopes that this is fixed to the glomeruli, particularly the basement membranes and also to the tubules and media of vessels. There may be no manifestations of illness, however, until after some days, when proteinuria, edema, and other manifestations of nephritis appear. The antibodies to rabbit kidney from the goose serum constitute a protein foreign to the rabbit, they stimulate the production of anti-goose antibodies in the rabbit which combine with their corresponding antigen, elements of the goose serum still fixed to the rabbit's kidney cells. A local hypersensitive reaction ensues which results in the nephritis. As others have pointed out, it is not the simple direct action of the antibody on the cells but the abnormal and violent reaction of the host to the antibody that causes the injury to the kidney cells.

Development of anti-kidney iso-antibodies by injection into another animal of the same species, e.g. rabbit, has been reported by a number of investigators. Some adjuvant is helpful and may be necessary. Vorlaender [15] believes that autosensitization occurs only if the tissue of the host has been altered.

Baxter and Goodman [17] carried out similar experiments, producing antisera for rat kidney in rabbits. Injection of this serum into rats caused serious and often fatal nephritis. The antibodies could be adsorbed and removed from the serum by fresh rat kidney suspensions but not by those from a rabbit or a dog and not by boiled extracts. Fresh tissue from rat lung or placenta was equally as effective as from kidney. These antibodies were specific as to species but not as to organ.

Liu and McCrory [18] investigated a large number of human sera for antibodies to human kidney, utilizing agglutination of tanned sheep red cells coated with human renal antigen. Significant reactions were reported with 71% of 35 cases of acute glomerulonephritis and 89% of 54 cases of the nephrotic syndrome. Weaker reactions were also often obtained with extracts of other organs. Occasional reactions, usually in lower titer, were observed in some other diseases, including acute rheumatic fever. Some of Vorlaender's observations [16] are confirmatory.

[14] Schmidt, H.: Auto-antikörper, Verhandl. deutsch. Gesellsch. inn. Med., Kong. **60**: 232–242, 1954.

[15] Vorlaender, K. O.: Neuere Ergebnisse zum Auto-immunisierungsproblem, Verhandl. deutsch. Gesellsch. inn. Med., Kong. **60**: 242–249, 1954.

[16] Vorlaender, K. O.: Über der Nachweis komplementbindender Auto-antikorper bei Nieren- und Lebererkrankungen, Ztschr. f. d. ges. exper. Med. **118**: 352–372, 1952.

[17] Baxter, J. H., and Goodman, H. C.: Nephrotoxic serum nephritis in rabbits. I. Distribution and specificity of the antigen responsible for the production of nephrotoxic antibodies, J. Exper. Med. **104**: 467–485, 1956.

[18] Liu, C. T., and McCrory, W. W.: Autoantibodies in human glomerulonephritis and nephrotic syndrome, J. Immunol. **81**: 492, 1958.

As noted by several investigators, it is practically impossible to secure an organ suspension consisting solely of its specific glandular cells. Some connective tissue and vascular tissue from capillaries and smaller vessels are also present and doubtless stimulate specific antibody formation. These presumably would be similar, from whatever organ they were derived, and they might explain much of the overlapping.

As pointed out by Schmidt,[14] such common antibodies might be absorbed from such a serum by a suspension of appropriate tissue and thus make possible proof of residual specific organ antibodies, although this is obviously a complicated technical procedure.

Auto-antibodies have also been reported in some diseases of the liver. Gear,[6] for example, noted that serum from a subject convalescent from viral hepatitis gave a positive precipitin reaction with serum from one in the acute phase. It was soon found that the antigen in this reaction was not the virus but derivatives of liver tissue. Normal liver extract was equally active. He also found that an extract of the liver of a monkey dead of yellow fever stimulated antibody formation in another monkey, but liver from a normal monkey did not. Here too some alteration of the cells was required to make them auto-antigenic. Gajdusek [10] has more recently reported a study of human sera from many sources for the presence of auto-antibodies to extracts of different normal human organs. He found positive complement fixation reactions rare in normal controls and in a group of miscellaneous diseases, but these occurred with significant frequency in some types of hepatic disease, in collagen diseases, especially disseminated lupus, and also in some cases of acute rheumatic fever, rheumatoid arthritis, glomerular nephritis and nephrosis, and in some cases of "paraproteinemia." Positive reactions were common in severe acute and chronic viral hepatitis, in nutritional (alcoholic) hepatitis, and in chronic nonobstructive biliary cirrhosis, but not usually in obstructive types. There was little or no organ specificity found. Sera from cases of hepatitis reacted as well or better with kidney extract than with liver extract, and often with that of other organs also—skeletal and cardiac muscle, lung, spleen, thyroid, and adrenal. They also reacted well with extracts of rat's organs.

The active agent in the serum resembled ordinary antibodies in their resistance to heat, to storage, in their capacity to be adsorbed and eluted, and on electrophoretic tests were found in the slow moving gamma globulins. Differential centrifugation of the antigenic extracts showed most activity in the fraction containing fine particulate material, mitochondria, microsomal constituents, threads of desoxyribonucleic acid.

Vorlaender [16] has also reported finding auto-antibodies in cases of hepatic disease.

In chronic ulcerative colitis auto-antibodies have been reported in individual cases by several observers. Recently Broberger et al.[19] reported

[19] Broberger, O., and Perlman, P.: Autoantibodies in human ulcerative colitis, J. Exper. Med. **110**: 657–674 (Nov.) 1959.

a study of 30 severe cases in children, half of whom had "extracolonic manifestations." He used phenol water extracts of colon and of various other organs and obtained positive precipitin reactions in 22 of the 30 cases with colonic extracts, of which four were positive with liver and six with renal extracts. Positive agglutination reactions were obtained in 28 of 30, using red cells coated with colonic extract, less often with liver or renal extract. A few reactions were obtained in other diseases, such as rheumatoid arthritis and nephritis. The active agent was in the gamma globulin fraction. He regards this as confirmatory evidence of an immunologic disorder, but he points out that no direct evidence exists that this antibody directly injures the cells. He was unable to detect any injury when the serum was added to fetal colonic tissue cultures. Similar antibodies active on colonic extracts were obtained in substantial concentration in saline extracts of regional (abdominal) lymph nodes, presumably a site of their production if they are real antibodies.

Systemic lupus erythematosus (SLE) has come to be regarded as the "auto-immune disorder par excellence." [20] Many of its varied clinical manifestations are highly suggestive of this. As to direct evidence, this is most convincing in the case of the hematologic disorders. An acquired hemolytic anemia often appears in lupus identical with the "idiopathic auto-immune" form, with the same type of hemolysins. The same is true of the thrombocytopenic purpura and it may well be also of the severe granulocytopenias of lupus, although the direct evidence of such antileukocytic antibodies is not very convincing. The evidence has been well reviewed by Dameshek.[20]

As to the injuries suffered by other tissues, the vasculitis resembles in many ways the lesions which have been produced experimentally by various hypersensitive reactions. Widespread injury to the vessels from some auto-antibody would well explain the equally widespread distribution of the lesions. There is no direct experimental proof, however, of such an action.

Positive serologic reactions have been obtained, however, between serum of lupus patients and extracts of various normal human tissues, similar to those just noted in several other diseases. Gajdusek,[11] e.g., examining 27 specimens from 12 patients with eight different antigens, obtained positive reactions with one or more antigens in 10, with some of them in high titer. Vorlaender [13] noted similar reactions of lupus serum with extracts of liver, kidney and heart which became negative while treated with steroids and recurred when these were stopped.

Failure to secure direct evidence may be due to lack of any effective technic to demonstrate antibody that is fixed to tissue cells. Assuming that cellular injury by auto-antibodies is an important etiological factor, it is surely fixed antibody that inflicts the injury, not the circulating antibody. This is borne out by the cases without circulating antibody and by the lack of correlation between its presence or titer and the stage of the disease, its

[20] Dameshek, W.: Systemic lupus erythematosus: a complex auto-immune disorder, Ann. Int. Med. **48**: 707–730 (Apr.) 1958.

acuteness or severity, the type of lesions or with other laboratory abnormalities.

Under special experimental conditions, antibodies can be absorbed from active sera by suitable suspensions of tissue cells, they can then be eluted from the cells and recombined with other cells, like the autohemolysins.[14] Possibly some technic along this line may eventually be worked out suitable for application to lupus patients.

Quite apart from the circulating antibodies so demonstrated, many serologic reactions of abnormal type have been encountered with lupus sera. These include positive Coombs' tests for autohemolysins, cephalin-cholesterol flocculation tests, cold agglutinations, and occasionally the rheumatoid factor, none of which have been proved to have primary pathogenic significance. The most extensively studied is the well known L. E. factor, a fraction of the gamma globulin not present in normal serum, which, perhaps after some initial injury to the cell, brings to culmination the nuclear alterations resulting in the L. E. cells. This factor is believed by Conley [21] to be distinct from these other antibodies. Both desoxyribonucleic acid (DNA) and nucleoproteins of the nucleus are necessary for this reaction. At first it was thought that the primary reaction was a specific antibody reaction between L. E. factor and DNA, but recent work indicates a primary reaction with the nucleoprotein, the changes in DNA being secondary. The latter is necessary, however, since prior application of desoxyribonuclease prevents the reaction.

Deicher et al.[22] have reported a study of the reactions between lupus sera and purified DNA. He obtained positive precipitin and complement fixation reactions in eight of 14 patients. DNA from any source was suitable. The precipitating factor migrated with the gamma globulins. Because serum from which the DNA precipitate had been removed caused the formation of L. E. cells and for other reasons they concluded that the precipitating factor and the L. E. factor are different gamma globulins.

By using fluorescent antibody in specific antisera to lupus gamma globulin, the active substance, presumably L. E. factor, was found in the nuclei of leukocytes beginning to undergo the characteristic changes, and in the lupus bodies, both extracellular and intracellular.[23] This may be absorbed by the nuclei of tissue cells from various normal human organs.[24] Positive reactions were also obtained with material in the hyaline thrombi, in the wire loop lesions and in the fibrinoid deposited or formed in the ground substance of the connective tissue [23] (and now known not to be derived from

[21] Conley, C. L.: The L. E. cell test, J. Chron. Dis. **5**: 275, 1957.

[22] Deicher, H. R. G., Holman, H. R., and Kunkel, H. G.: The precipitin reaction between DNA and a serum factor in systemic lupus erythematosus, J. Exper. Med. **109**: 97–114 (Jan.) 1959.

[23] Mellors, R. C., Ortega, L. G., and Holman, H. R.: Role of gamma globulin in the pathogenesis of renal lesions in systemic lupus erythematosus and chronic membranous glomerulonephritis, with an observation on the lupus erythematosus cell reaction, J. Exper. Med. **106**: 191–202, 1957.

[24] Holborow, E. J., Weir, D. M., and Johnson, G. D.: A serum factor in lupus erythematosus with affinity for tissue nuclei, Brit. M. J. **2**: 732, 1957.

collagen). Proof that SLE gamma globulin not found in normal serum can combine with tissue cells as well as with leukocytes and that it is found, probably in a precipitate, in the characteristic lesions of the connective tissue greatly strengthens the suspicion of its pathogenetic significance. There is, however, no real proof that L. E. factor is etiologically important. It is often a relatively late manifestation of the disease, and as emphasized by Harvey et al.[25] there is no good correlation between its presence or titer and the clinical manifestations of the disease.

In most cases auto-antibodies have been produced experimentally only with altered or damaged cells. If injured tissue of the host is capable of stimulating an "auto-immunizing reaction," there must be innumerable opportunities for such reactions to occur. They should be much more frequent than they are unless there was some mechanism in the body to prevent them. The reticuloendothelial tissues must be able to "distinguish" in some way between familiar (autologous) and strange (heterologous) proteins. Burnet [26] has suggested that such tissues as are expendable, regularly ingested and destroyed like blood cells, must have some indication of their compatibility, perhaps a "selfmarker" of some sort, to ensure their recognition. Cells from fixed tissues not ordinarily reaching the reticuloendothelial cells might lack such markers, "appear" strange, and excite auto-antibody production. The precise configuration of the sidechains in the protein molecules might conceivably serve as such a marker. If such a system exists, disturbances of function might easily occur, with lack of "recognition," and hostile reception of what should be familiar substances. It has also been suggested [27] that the process may be initiated by a reaction to some heterologous protein and then continue as an auto-immunizing reaction to altered nuclear constituents of the host's cells.

There can be no doubt that reactions of this general nature do occur, but they are still inadequately understood. Evidence that the active substances are auto-antibodies is persuasive but still for most of them indirect. Very little is known regarding the antibodies fixed to tissue cells, presumably the chief source of injury. The "immunity" to isografts which is exceptionally strong seems due entirely to alterations in the tissue cells. No circulating antibodies have been detected. The circulating antibodies in these diseases on which attention has perforce been largely fixed may often be accessory phenomena of secondary importance, indications of disturbed function but not necessarily a direct source of injury themselves. The intensive investigations now in progress in this field should soon solve many of these problems.

PAUL W. CLOUGH, M.D.

[25] Harvey, A. M., Schulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H.: Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases, Medicine **33**: 291, 1954.

[26] Burnet, F. M., and Fenner, F.: The production of antibodies, monograph of the Walter and Eliza Hall Institute, 2nd Ed., 1949, Macmillan and Co. Ltd., Melbourne, Australia.

[27] Bardawil, W. A., Toy, B. L., Galens, N., and Bayles, T. B.: Disseminated lupus erythematosus, scleroderma and dermatomyositis as manifestations of sensitization to DNA-protein. I. An immunohistochemical approach, Am. J. Path. **31**: 607, 1958.

REVIEWS

The Physiology and Treatment of Peptic Ulcer. Edited by J. GARROTT ALLEN, M.D., Department of Surgery, University of Chicago. 236 pages; 16 × 24 cm. The University of Chicago Press, Chicago. 1959. Price, $7.50.

This small volume is a collection of papers written by men who have been students or clinical associates of Dr. Lester R. Dragstedt.

The first four chapters pertain to the physiology of gastric secretion and recount selected experiments performed by Dr. Dragstedt and his associates. The acid-pepsin concept of peptic ulcerogenesis is developed from these studies and there follow presentations of ulcer therapy based upon this concept.

X-ray diagnosis and treatment of peptic ulcer are discussed and the results of gastric irradiation are presented, no associated morbidity having been noted to date. The difficulty of attaining complete suppression of interdigestive acid production by pharmacologic agents is reaffirmed.

There is medical and surgical agreement that gastric aspiration therapy of perforated acute duodenal ulcer may properly be applied more widely than at present, while resection is preferred for perforated chronic ulcer.

Gastric ulcer, its pathogenesis, treatment and its differentiation from malignant disease are capably discussed.

The book closes with a reprint of Dr. Dragstedt's engaging and concise essay, "What Would I Do if I Had an Ulcer?"

The stated limitation of scope of the book denies full space to proponents of local vascular factors in peptic ulcerogenesis.

An excellent bibliography is appended. The text is well written and is easily followed. The illustrations are pertinent and clearly presented. The book should be useful to all who meet the ulcer problem in practice.

V. M. S.

"Allergic" Encephalomyelitis. Edited by MARIAN W. KIES, Ph.D., Chief, Section on Biochemistry, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland, and ELLSWORTH C. ALVORD, JR., M.D., Associate Professor of Neurology and Pathology, Baylor University College of Medicine, Houston, Texas. 576 pages; 23.5 × 15.5 cm. Charles C Thomas, Publisher, Springfield, Illinois. 1959. Price, $13.50.

This book presents the proceedings of a symposium held in 1957 under the sponsorship of the National Advisory Neurological Diseases and Blindness Council and the National Institute of Neurological Diseases and Blindness. Fifty-nine investigators, well-known for their contributions to the field of "allergic" encephalomyelitis, have participated in the compilation of this comprehensive review of the many problems associated with these disorders. Apologies have been made for use of the word "allergic" by emphasizing that the mechanism by which these diseases are produced is still unknown.

The first section of this volume deals with clinico-pathologic correlations and comprises six chapters which occupy about one third of the book. A summary of the methods employed in the study of histopathologic changes observed in experimental allergic encephalomyelitis (EAE) is presented. Pleomorphism of the experimentally-induced lesions is emphasized and a classification of lesions is accompanied by illustrative and descriptive examples of each. It is proposed that histologic

pleomorphism is the result of many factors including host variations, rapidity of the causative process, contributing physiologic anomalies of endocrine function and trauma as well as secondary histopathologic factors of a metabolic and physical nature. Comparison of experimental studies with various human diseases suggests that acute circumscribed and disseminated encephalomyelitis or acute multiple sclerosis and the more chronic disease resulting in sclerosis are variations of the same process. Rabies post-vaccinal encephalitis is discussed in detail with a summary of experiences in various parts of the world. Although two forms of this complication of rabies immunization are recognized, separation of cerebral and spinal types seems somewhat artificial in view of simultaneous occurrence of these lesions. Of some interest was the frequent occurrence of personality changes and neurologic residue in recipients of rabies vaccine in Japan during the period prior to 1957 when Calmette vaccine was employed. Similarities between acute multiple sclerosis and rabies post-vaccinal encephalomyelitis are noted. Although correlation among clinical manifestations, circulating antibody, antigen and skin sensitivity is wanting, the consensus seems to be that this disease is an immunobiologic phenomenon. Genetic and nutritional aspects of experimental allergic encephalomyelitis and species variation noted in the experimental disease are reviewed in separate chapters. The nature of encephalitogenic fractions of cerebrum and cord is discussed in seven chapters contributed by experts in this field. Activity of the proteolipid fractions of Folch and Lees is compared with water-soluble encephalitogenic fractions described by Roboz. All of the authors conclude that multiple nervous-tissue components seem to be isolated in the production of EAE and that species variation is quite marked. The importance of Freund type adjuvants in producing this disease in lower animals is, of course, emphasized throughout the book.

Immunological aspects of experimental allergic encephalitis are presented in the last section of this book. These include excellent discussions of organ specificity, attempts at passive transfer of sensitivity to nervous tissue, the role of adjuvants and tolerance to paralytogenic effects of nervous tissue in the experimental animal. Arguments for and against an immunobiologic phenomenon as a cause of experimental allergic encephalomyelitis as well as various post-infectious encephalomyelitides are presented lucidly in this section. The entire symposium has been summarized by Dr. Alvord who concludes that elucidation of the etiologies of EAE will be a complicated quantitative problem involving precise definition of host factors, encephalitogenic components of nervous tissue and immunologic phenomena associated with the disease.

This book is composed of well written papers which have been edited superbly. Each presentation is accompanied by very interesting discussion and comprehensive bibliographies. In addition, the choice of illustrative material has been excellent. The clinician, who may find the technical discussions of only passing interest, will nevertheless profit from his reading of those sections wherein attempts have been made to correlate clinical and laboratory aspects of this syndrome. Every student of neurologic disorders as well as those interested in diseases of hypersensitivity will find this volume an invaluable addition to his library.

FRED R. MCCRUMB, JR., M.D.

Antithrombotic Therapy. Modern Medical Monographs 20. By PAUL W. BOYLES, M.D. 131 pages; 22.5 × 14 cm. Grune & Stratton, Inc., New York. 1959. Price, $5.00.

On initially picking up this little volume there is apt to be a quizzical lifting of the brow. With the rather inclusive and ambitious title "Antithrombotic Therapy,"

it is noted that the reading matter of the monograph measures barely over one quarter inch in thickness.

Moreover, the author admits in his preface that he is "invading" two controversial fields of medicine"—the mechanism of blood clotting and the treatment of thromboembolic diseases. Certainly, then, no one should "invade" this field with such stark brevity unless he possesses a unique gift for expounding his subject with fundamental thoroughness, yet tersely stripping down the material of all non-essentials. And, to this reviewer's satisfaction and pleasure, Dr. Boyles has done just this! Crowded into this little volume one will find a succinct compilation of all that is new and generally accepted on the factors involved in blood coagulation. As to treatment, anticoagulant therapists might here wish for a little more detailed discussion. However, in the therapeutic area controversy still wages and the pros and cons of argument never lend to brevity. Nevertheless, the fundamentals of adequate treatment certainly are given.

A final chapter on "Thrombolytic Therapy" is most welcome. All of these newer agents, designed to lyse out an already formed clot, are discussed, together with their possible mode of action, toxic side-effects, etc. Concerning one of these agents, Dr. Boyles might be quoted: "It seems likely that fibrinolysin combined with anticoagulants will be prescribed for all types of acute thrombotic episodes when a nontoxic preparation becomes available."

In an Addendum, detailed laboratory tests for the various clotting factors together with several valuable tables are given.

Irrespective of physical size this little volume contains nothing but essential, authoritative information. For those interested in this field it is a "best buy."

H. R. P.

Proceedings of the World Congress of Gastroenterology and the Fifty-ninth Annual Meeting of the American Gastroenterological Association. Vols. I and II. 1363 pages (both volumes); 26 × 17.5 cm. The Williams & Wilkins Co., Baltimore. 1959. Price, $20.00.

These two handsomely bound volumes represent the contributions of many of the participants in the World Congress of Gastroenterology held in Washington, D. C., in May 1958. The work is purported to provide a broad, comprehensive view of gastroenterology in its present state of development. The material consists of manuscripts, original contributions, and panel discussions by investigators and clinicians from all parts of the medical world. Abstracts and summaries have been inserted where full publication has not been feasible. Publication in foreign language is limited to 11 papers. There is no doubt that the editorial task was a great one and that scrutiny was difficult.

As might be suspected, because of diverse origin, the quality of the content fluctuates greatly. Frequently, the space allotted to a subject is not commensurate with its importance. Actually, there are few new contributions and most of the important matter has been published elsewhere. Interest is more likely to be stimulated by the ethnic and geographic differences in the patterns of digestive tract disease and nutritional disturbances, than by the rehashing of concepts and arguments, in some instances already outdated.

It is difficult to assess the value of these volumes for physicians other than those with a special interest in gastroenterology, but it is suspected that among them there will be few subscribers.

J. E. K.

A Primer of Water, Electrolyte and Acid-Base Syndromes. By EMANUEL GOLDBERGER, M.D., F.A.C.P., Lecturer in Medicine, Columbia University. 322 pages; 21 × 14 cm. Lea & Febiger, Philadelphia. 1959. Price, $6.00.

This book is based on a series of lectures given by Dr. Goldberger and as such is written in a style that is easy to follow. Each chapter is organized in sections that are commonly used in larger texts, beginning with a definition of the syndrome, followed by discussion of etiology, pathological physiology, symptoms, signs, etc. The use of fluids in surgical and pediatric patients is briefly discussed and a chapter devoted to a description of the many solutions available.

Treatment in medicine is often a matter of opinion. One may not always agree with specific methods but this book does present rational, well outlined steps for handling specific problems. It is a valuable source of information for all who are directly involved in the care of the hospitalized patient.

DAVID A. LEVY, M.D.

Symposium on Pulmonary Ventilation. Edited by Dr. R. P. HARBORD and Professor R. WOOLMER. 109 pages; 23 × 14.5 cm. The Williams & Wilkins Co., Baltimore. 1959. Price, $4.00.

This is an edited version of a symposium on pulmonary ventilation held in Leeds, February 19, 1958, under the auspices of the *British Journal of Anaesthesia.* The papers reported are: "Lung Gas Sampling and Analysis during Anaesthesia," P. W. Ramwell; "Observations on Sampling Expiratory Gases during Artificial Respiration," R. P. Harbord and I. S. Bruce; "Problems of Pulmonary Ventilation in the Newborn," I. Donald; "A Clinical Note on the Difficulties of Maintaining Adequate Pulmonary Ventilation during Hypothermia," T. C. Gray; "Management of Pulmonary Ventilation in Emphysematous Subjects in the State of Carbon Dioxide Narcosis," P. Hugh-Jones; "Mechanisms of Airway Obstruction," E. J. Moran; and "Discussion on Measuring Respiratory Ventilation." Each is followed by a discussion by well-known British students of the subject or its ramifications.

Few will be interested in all of the volume, but many will be interested in certain papers. For instance, the report by Prof. Donald would fascinate most obstetricians and would certainly interest all physicians who are parents.

Of general interest is the candor of the reported discussion; apparently, the British are willing to admit in print that they question the speaker's views.

B. W. A.

Handbook of Physiology. Section 1: Neurophysiology. Volume I. Editor-in-Chief: JOHN FIELD; Section Editor: H. W. MAGOUN; Executive Editor: VICTOR E. HALL. 779 pages; 29 × 22 cm. The Williams and Wilkins Company, Baltimore. 1959. Price, $22.00.

This sizable book of more than 700 pages forms a part of a series in which the present day knowledge and concepts of physiology are presented. This volume, the first in the Neurophysiology section, covers the historical development of neurophysiology; the physiology of the neuron; brain potentials and sensory mechanisms, including a separate group of essays dedicated to vision. The presentations are prepared by investigators who are foremost in their respective fields. In spite of the difficulties of the subject matter, the great majority of the authors have been able to keep their text clear and readable even for those not familiar with the intricate details of their subject.

Unfortunately, however, some of the concepts presented have been outdated

already by more recent discoveries, an inevitable shortcoming of handbooks of this type. The illustrations as well as the print itself are excellent, which makes the consultation of this standard work even more enjoyable. All these virtues of the present volume undoubtedly create great expectations regarding the second volume in this section.

Obviously this book should be highly recommended to everybody interested in neurophysiology and the current concepts in this fast moving field. From a clinical point of view, however, the immediate use of this handbook might be somewhat limited. On the other hand, for those active in the field of clinical neurology and related specialties it will prove itself undoubtedly of great value as an unequaled source of up-to-date basic information. It is for this reason that this book is highly recommended to everybody dealing with disorders of the nervous system.

HENRICUS G. J. M. KUYPERS

Cancer in Families: A Study of the Relatives of 200 Breast Cancer Probands. By DOUGLAS P. MURPHY, M.D., and HELEN ABBEY, Sc.D. 76 pages; 21.5 × 14 cm. Published for the Commonwealth Fund by the Harvard University Press. 1959. Price, $2.50.

One of the commonly accepted generalizations concerning the epidemiology of cancer is that this disease occurs more frequently among relatives of a person with cancer than among relatives of a person who does not have cancer. If it can be demonstrated that familial aggregation of cancer takes place, and only in certain types, strong clues concerning the etiology of cancer can follow. However, research in this area is difficult and has been characterized by serious limitations in many instances.

The authors of the report reviewed here, following an evaluation of existing studies, designed an investigation which would avoid the weaknesses uncovered in their survey of the literature, which were essentially (1) differences in the quality of information provided on a recall basis between cancer probands and their controls, (2) differences in the age, economic or other environmental characteristics of the cancer and control families compared.

This investigation is concerned with the extent of cancer found among relatives of 200 cancer probands and 198 control persons. The cancer probands were white women admitted for cancer of the breast. Following a comparison of the cancer and control groups in respect to education, economic and other background characteristics, the frequency of cancer is presented in simple concise tables. Only one conclusion need be cited, namely that no familial aggregation of cancer could be found in this study.

This book, a brief monograph of 76 pages, should be read by all who are closely connected with the epidemiology of cancer and by the diagnostician who may have formed strong impressions on the high cancer risk or lack of it which exists among relatives of persons with diagnosed cancer.

MATTHEW TAYBACK, ScD.

Health Statistics from the U. S. National Health Survey, Series B-8 and B-10: Disability Days, United States, July 1957 to June 1958. 68 pages; 26 × 20 cm. (paper-bound). U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. 1959. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 40 cents.

In 1956 there was established, within the Public Health Service, the U. S. National Health Survey, which was authorized to do a continuing survey of the health conditions in the general population.

The "A" series of publications covers the origin, program, statistical design and definitions of the U. S. National Health Survey and the Health Household Interview Survey. The "B" series provides data on the results of these surveys. Series B-8 covers persons injured by class of accident in the United States for the fiscal year 1958, and series B-10 covers the disability days for that same fiscal year.

The health statistics emanating from this continuing study will be of particular importance to those persons responsible for the direction of operating health agencies.

G. E.

The Investigation of the Relative Function of the Right and Left Lung by Bronchospirometry: Technique, Physiology and Application. By FRANK BERGAN, M.D. 145 pages; 24 × 17.5 cm. (paper-bound). Grune & Stratton, Inc., New York. 1958. Price, $4.50.

The author did his work in the Department of Respiratory Physiology at the University of Oslo. The organization of his work is along classic lines, with acknowledgment of the influence of thoracic surgical advances upon the development of this procedure. The author includes description of the technic and instruments, an evaluation of the work-loading test during the procedure in the supine position, significance of position change, and a discussion of the value of the method in clinical work as a preoperative investigation, as well as its usefulness postoperatively in assessing function changes as a result of surgery. The author refers to the historical aspects of the procedure, noting that the separate registering of lung function has been done on animals since 1889.

Since 1951 the author has performed function studies on 300 patients—the majority preoperatively on patients suffering from pulmonary tuberculosis.

Reference is made to right heart and pulmonary artery catheterization for pressure determinations. The usual spirometric information is included. Some detail of the patient preparation, anesthesia, intubation, etc., is given. Possible technical errors are mentioned, including clinical examples. Possible complications are described. Contraindications to the procedure are mentioned. Methods for the calculation of results are given.

The clinical usefulness of this procedure is evaluated largely on the basis of references to the work of others. For instance, the author carried out pre- and postoperative studies in only 16 cases between 1951 and 1956. The effect of decortication is evaluated on the strength of pre- and postoperative results in five cases.

However, there are interesting descriptions of changes in oxygen consumption, ventilation, functional residual capacity occurring in various positions, and an evaluation of work-loading tests in this procedure.

The monograph is a useful summary of work done largely by others in establishing the procedure of differential bronchospirometry. Seventy references are provided.

R. C. D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Arteriopatie Obliteranti Degli Arti Inferiori. By G. MARCOZZI, S. MESSINETTI and G. A. RICCI. 195 pages; 25 × 17.5 cm. 1959. Edizioni Mediche e Scientifiche, Rome. Price, L. 5.800.

Arthritis: Medical Treatment and Home Care. By JOHN H. BLAND, M.D.; illustrated by GEORGE DALY. 208 pages; 21.5 × 14.5 cm. 1960. The Macmillan Company, New York. Price, $4.95.

Chronic Respiratory Conditions Reported in Interviews, United States, July 1957–June 1958. Statistics on Prevalence of Chronic Respiratory Conditions and Associated Disability by Age, Sex, Medical Attention, and Type of Condition. Based on Data Collected in Household Interviews During the Period July 1957–June 1958. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584–B12. 32 pages; 26 × 20 cm. 1959. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. at 30¢.

Diagnosis and Treatment of Tumors of the Chest. Sponsored by the American College of Chest Physicians. Editorial Board: DAVID M. SPAIN, M.D., Chairman, Brooklyn, N. Y., Editor-in-Chief; SEYMOUR M. FARBER, M.D., San Francisco, California; PAUL H. HOLINGER, M. D., Chicago, Illinois; HERBERT C. MAIER, M.D., New York, N. Y.; EDGAR MAYER, M.D., New York, N. Y.; ALTON OCHSNER, M.D., New Orleans, Louisiana; and COLEMAN B. RABIN, M.D., New York, N. Y. 371 pages; 26 × 18 cm. 1960. Grune & Stratton, New York. Price, $14.75.

A Digest of State Air Pollution Laws. By SAMUEL M. ROGERS, Program Advisor, Air Pollution Engineering Program; and SIDNEY EDELMAN, Assistant Chief, Public Health Division, Office of the General Counsel, U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. 117 pages; 26 × 20 cm. (paper-bound). 1959. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 75¢.

Drugs in Current Use, 1960. Edited by WALTER MODELL, M.D., F.A.C.P., Associate Professor, Clinical Pharmacology, Cornell University Medical College. 152 pages; 21 × 14 cm. 1960. Springer Publishing Company, Inc., New York. Price, $2.25.

European Technical Conference on Food-Borne Infections and Intoxications, Geneva, 16–21 February 1959: Report. World Health Organization Technical Report Series No. 184. 18 pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

The Extremities. 2nd Ed. By DANIEL P. QUIRING, Ph.D., Late Head of the Anatomy Division, Cleveland Clinic Foundation, and Associate Professor of Biology, Western Reserve University; Second Edition revised and edited by JOHN H. WARFEL, Ph.D., Assistant Professor of Anatomy, The University of Buffalo, School of Medicine, Buffalo, N. Y. 120 pages; 24 × 15.5 cm. 1960. Lea & Febiger, Philadelphia. Price, $3.25.

La flebografia vertebrale transomatica. By G. MARCOZZI, S. MESSINETTI, L. SARACCA and M. COLOMBATI. 159 pages; 25 × 18 cm. 1959. Edizioni Mediche e Scientifiche, Rome. Price, L. 6.500.

From Magic to Science: Essays on the Scientific Twilight (Dover Book T390). By CHARLES SINGER. 253 pages; 20.5 × 13.5 cm. (paper-bound). This is a new Dover edition, first published in 1958; an unabridged republication of the first edition. Dover Publications, Inc., New York. Price, $2.00.

Fundamentals of Modern Allergy. Sponsored by the New York Allergy Society. Edited by SAMUEL J. PRIGAL, M.D. 690 pages; 23.5 × 15.5 cm. 1960. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $18.50.

Gestation: Transactions of the Fifth Conference, March 11, 12, and 13, 1958, Princeton, N. J. Edited by CLAUDE A. VILLEE, Ph.D., Associate Professor of Biological Chemistry, Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts. 262 pages; 24 × 16 cm. 1959. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $5.75.

Handbook of Physiology: A Critical, Comprehensive Presentation of Physiological Knowledge and Concepts. Section 1: *Neurophysiology.* Volume II. Editor-in-Chief: JOHN FIELD; Section Editor: H. W. MAGOUN; Executive Editor: VICTOR E. HALL. Total pages in Vols. I and II, 1,439; 29 × 22 cm. 1960. Published by American Physiological Society, Washington, D. C., and distributed by The Williams & Wilkins Company, Baltimore. Price, $20.00.

The Human Spine in Health and Disease. Anatomicopathologic Studies by GEORG SCHMORL, M.D.; Clinicoradiologic Aspects by HERBERT JUNGHANNS, M.D.; the first American edition, translated and edited by STAFAN P. WILK, M.D., and LOWELL S. GOIN, M.D. 285 pages; 29 × 20 cm. 1959. Grune & Stratton, New York. Price, $21.00.

Leukocyte Antigens and Antibodies. By ROY L. WALFORD, M.D., Assistant Professor of Pathology, University of California School of Medicine, Los Angeles, etc. 182 pages; 22.5 × 14 cm. 1960. Grune & Stratton, New York. Price, $6.75.

De Magnete (Dover Book S 470). By WILLIAM GILBERT; translated by P. FLEURY MOTTELAY. 368 pages; 20.5 × 13.5 cm. (paper-bound). This new Dover edition, first published in 1958, is an unabridged and unaltered republication of the P. Fleury Mottelay translation published in 1893. Dover Publications, Inc., New York. Price, $2.00.

The Medical Sourcebook: A Reference Handbook for Legal, Legislative and Administrative Personnel. By FRED A. METTLER, Ph.D., M.D., Sc.D. (Hon.), Professor of Anatomy, Columbia University. 1,000 pages; 25.5 × 18.5 cm. 1959. Little, Brown and Company, Boston. Price, $25.00.

Medieval and Renaissance Medicine. By BENJAMIN LEE GORDON, M.D., F.I.C.S. 843 pages; 21.5 × 14.5 cm. 1959. Philosophical Library, New York. Price, $10.00.

Modern Nutrition in Health and Disease: Dietotherapy. 2nd Ed. edited by MICHAEL G. WOHL, M.D., Chief of Human Nutrition, Division of Biological Chemistry, Hahnemann Medical College and Hospital, etc.; and ROBERT S. GOODHART, M.D., Scientific Director, The National Vitamin Foundation, Inc., etc.; with 59 contributors. 1,152 pages; 24 × 15.5 cm. 1960. Lea & Febiger, Philadelphia. Price, $18.50.

L'Ostruzione Intestinale (*Fisiopatologia e Clinica*). By PROF. EDMONDO MALAN; with the collaboration of A. AROLDI, F. ASCHIERI, V. DI GIOVANNI, G. JAPICHINO, V. MAGLIULO, C. MALCHIODI, A. MIANI, S. OCCHIPINTI, A. PUGLIONISI, F. SAVARESE, G. C. SERRA, S. SERRANO, G. TATTONI and N. ZINICOLA. 311 pages; 25 × 18 cm. 1959. Edizioni Mediche e Scientifiche, Rome. Price, L. 4.800.

Perspectives in Pediatric Virology: Report of the Thirty-third Ross Conference on Pediatric Research. 91 pages; 23 × 15 cm. (paper-bound). 1959. Ross Laboratories, Columbus, Ohio. Available on request.

Ring the Night Bell: The Autobiography of a Surgeon. By PAUL B. MAGNUSON; edited by FINLEY PETER DUNNE, JR. 376 pages; 21.5 × 14.5 cm. 1960. Little, Brown and Company, Boston. Price, $5.00.

The Story of Dissection. By JACK KEVORKIAN, M.D. 80 pages; 22.5 × 14.5 cm. 1959. Philosophical Library, New York. Price, $3.75.

MEDICAL NEWS

National Index on Deafness, Speech and Hearing

Gallaudet College and the American Speech and Hearing Association have established a National Index on Deafness, Speech and Hearing. The purpose of the National Index is to index and abstract all professional literature pertaining to deafness, speech and hearing and to make this material readily available to all interested persons. Not only will present and future literature be included, but also all of the relevant past literature. The National Index will make the collected material available through a regular professional publication. It is believed that the National Index will provide a necessary and useful service to all persons concerned with the problems of deafness, speech and hearing.

The National Index on Deafness, Speech and Hearing is made possible in part by a grant from the Office of Vocational Rehabilitation of the Department of Health, Education and Welfare.

Further information on the Index may be obtained by writing to:

Dr. Stephen P. Quigley, Director
National Index on Deafness, Speech and Hearing
Gallaudet College
Washington 2, D. C.

1959 A.C.P. Directory

The Directory of the College has been fully revised during the last nine months and brought up to date to November, 1959. It is in the final stages of printing. It will be sent free and automatically to all Life Members of the College. The pre-publication price was $9.00, postpaid. Many orders have long since been entered by members and their copies will be mailed immediately on completion of publication. The post-publication price is $12.00, postpaid. The Directory is cloth bound and will consist of some fourteen hundred pages.

The Residency Revolving Loan Fund of the American College of Physicians

The purpose of this Fund is to aid young physicians planning a future career in Internal Medicine, or specialties allied thereto, to pursue adequate graduate training as full-time residents, research assistants and/or fellows in accredited institutions, which training might otherwise not be available to them because of financial needs. The Committee may give some priority to candidates anticipating careers in academic medicine, although that shall not be a requirement.

Loans are limited to not more than $1,000.00; they shall be made only for living expenses incidental to the period of training. Loans may be made for varying periods of time, up to a maximum of five years; they may be repaid, in part or in full, at any time. No interest is charged for the first two years of the loan, or until completion of specialty training, whichever comes first; thereafter, simple interest shall be charged at the rate of 3% per annum for two years; 6% thereafter.

Applications shall be made on the official form supplied by the College. When the application is approved by the Committee, the borrower shall sign the official, non-negotiable contract form supplied by the College; co-signed by the wife, parent or guardian.

Announcements

The University of Minnesota announces a continuation course in intermediate Electrocardiography for General Physicians and Specialists, which will be held at the Center for Continuation Study on the University Campus from May 2 to 6, 1960. This course is intended primarily for physicians who are familiar with the basic principles of electrocardiographic interpretation and is to assist them in improving their ability in evaluating the more unusual and difficult electrocardiograms.

Guest speakers will include Doctors Henry J. L. Marriott, Associate Professor, Department of Medicine, University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, Maryland; and Louis Wolff, Assistant Clinical Professor, Department of Medicine, Harvard Medical School, Boston, Massachusetts. The remainder of the faculty will include members of the faculty of the University of Minnesota Medical School.

Lodging and meal accommodations are available at the Center for Continuation Study.

Continuation Course for Physicians

University of Minnesota

Center for Continuation Study

Minneapolis, Minnesota

Date

* May 9–11, 1960

Name of Course

Cardiovascular Diseases for General Physicians and Specialists

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The San Francisco-Stanford Hospital, in coöperation with the San Francisco Heart Association, announces a postgraduate conference, "Vector-Electrocardiography: Vector Interpretation of the Conventional Electrocardiogram," on Saturday, May 28, 1960, 9 a.m. to 5 p.m. Guest speaker: E. Grey Dimond, M.D., Professor of Medicine, University of Kansas Medical School. For information, write to Arthur Selzer, M.D., San Francisco-Stanford Hospital, Clay and Webster Streets, San Francisco 15, California.

* These dates for this course have been changed from February 8–10, 1960.

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The actions of Nilevar[4] in reversing a negative nitrogen balance—and therefore a negative protein balance—improving the appetite and increasing the sense of well-being can be expected to shorten the illness and the convalescence of these patients.

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1. Eisen, H. N., and Tabachnick, M.: Protein Metabolism, M. Clin. North America 39:863 (May) 1955. 2. Jamison, R. M.: General Nutritive Deficiency, Virginia M. Month. 83:67 (Feb.) 1956. 3. Goldfarb, A. F.; Napp, E. E.; Stone, M. L.; Zuckerman, M. B., and Simon, J.: The Anabolic Effects of Norethandrolone, a 19-Nortestosterone Derivative, Obst. & Gynec. 11:454 (April) 1958. 4. Batson, R.: Investigator's Report, Feb. 11, 1956. 5. Weston, R. E.; Isaacs, M. C.; Rosenblum, R.; Gibbons, D. M., and Grossman, J.: Metabolic Effects of an Anabolic Steroid, 17-Alpha-Ethyl-17-Hydroxy-Norandrostenone, in Human Subjects, J. Clin. Invest. 35:744 (June) 1956. 6. Brown, C. H.: The Treatment of Acute and Chronic Ulcerative Colitis, Am. Pract. & Digest Treat. 9:405 (March) 1958.

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"In our experience . . . administration of meprobamate brings prompt relief from muscle spasm and alleviation from concomitant anxiety. In all 197 patients treated, muscle relaxation was sufficient to permit surgical or non-surgical repair of the injury and to encourage rapid healing."

Wein, A.B.: Clin. Med. *6*:41 (Jan.) 1959.

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CARDIOVASCULAR DISEASE

"On control of the emotional complications [with meprobamate in 41 varied patients], treatment in every case was less intensive and prolonged than ordinarily would have been expected."

Friedlander, H.S.: Am. J. Card. *1*:395 (March) 1958.

EQUANIL® MEPROBAMATE, WYETH





CHRONIC HEADACHE

"Meprobamate was found of considerable value in reducing the tension component of chronic headache, and thus decreasing the frequency and severity of attacks. No intolerance, dependence, or side effects were noted. . . ."

Blumenthal, L.S., and Fuchs, M.: Am. Pract. & Digest Treat. *9*:1121 (July) 1958.

EQUANIL® MEPROBAMATE, WYETH

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"Meprobamate alone or in combination with reduced amounts of previously used hypnotics or milder non-habit-forming hypnotics enabled patients to obtain a deeper, more restful sleep without unpleasant after effects."

Millen, F.J.: Wisconsin M. J. *56*:198 (April) 1957.

EQUANIL® MEPROBAMATE, WYETH





PREMENSTRUAL TENSION

In combination with a mild diuretic, "meprobamate in our series completely or virtually relieved overt symptoms of premenstrual tension in 86 of 100 women." Before therapy "...85 per cent had temper tantrums and outbursts of fitful and inappropriate crying."

Podolsky, E.: Journal-Lancet 79:318 (July) 1959.

EQUANIL® MEPROBAMATE, WYETH

PEDIATRIC BEHAVIOR PROBLEMS

"The boys [65 per cent] felt happier, more easy-going, content, and passive, and were less inclined to fight. They enjoyed more play activities and social contacts. They appeared to be more relaxed and calm, showed marked improvement in social behavior, and marked signs of a 'softening process' . . . ." Rawitt, K.C.: Am. J. Psychiat. *115*:1158 (June) 1959.

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ALCOHOLISM

"Results were satisfactory in the great majority [of 93 patients]. A safe, non-habit-forming relaxant, meprobamate . . . is useful for relief of anxiety, tension and depression, particularly following episodes of acute alcoholism."

Turvey, S.E.C.: Canad. M.A.J. 74:863 (April) 1956.

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Throughout the practice of medicine...

EQUANIL is a fundamental aid in the control of tension, both mental and muscular. Hundreds of published studies attest to its efficacy and wide range of usefulness.

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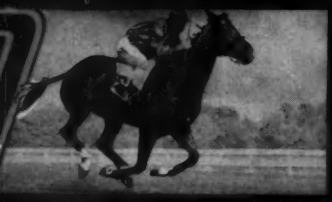
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Relieves interval pain[2,4]—reduces joint swelling[3]—improves mobility.[2]

References:
1. Yü, T. F., Burns, J. J., and Gutman, A. B.: Arth. & Rheumat. *1*:532, 1958. 2. Gutman, A. B., and Yü, T. F.: Bull. N. Y. Acad. Med. *34*:287, 1958. 3. Kersley, G. D., Cook, E. R., and Tovey, D. C. J.: Ann. Rheumat. Dis. *17*:326, 1958. 4. Ogryzlo, M. A., and Harrison, J.: Ann. Rheumat. Dis. *16*:425, 1957.

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CLINICAL NOTES

HEMATOLOGY

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ASTRAFER® (ASTRA) I.V.

COMPOSITION A soluble, high-molecular, iron carbohydrate complex, equivalent to 20 mg. trivalent iron per cc., not to be confused with saccharated iron complexes.

PROPERTIES ASTRAFER® I.V. is a neutral solution and does not irritate the intima. It is relatively free from the side reactions previously encountered with other intravenous iron preparations. 70-100% of the iron supplied by this agent is utilized in hemoglobin synthesis. Patient improvement is marked by a measurable sense of well being, and is seen coincidentally with the return to normal of serum iron and hemoglobin levels, usually beginning with the third or fourth injection.

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1. Kestler, O: In The Pharmacology and Clinical Usefulness of Carisoprodol. Wayne State University Press, Detroit, 1959. 2. Berger, F. M.; Kletzkin, M.; Ludwig, B. J.; Margolin, S., and Powell, L. S.: J. Pharm. Exp. Ther. *127*:66 (Sept.) 1959. 3. Spears, C. E. and Phelps, W. M.: Arch. Pediat. *76*:287 (July) 1959. 4. Phelps, W. M.: Arch. Pediat. *76*:243 (June) 1959. 5. Friedman, A. P.; Frankel, K., and Fransway, R. L.: Papers presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc. ,New York, Sept. 30, 1959. 6. Kuge, T.: Unpublished reports. 7. Ostrowski, J. P.: Orthopedics (In Press).

Literature and samples on request

Also available on request: The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959. (185 pages)

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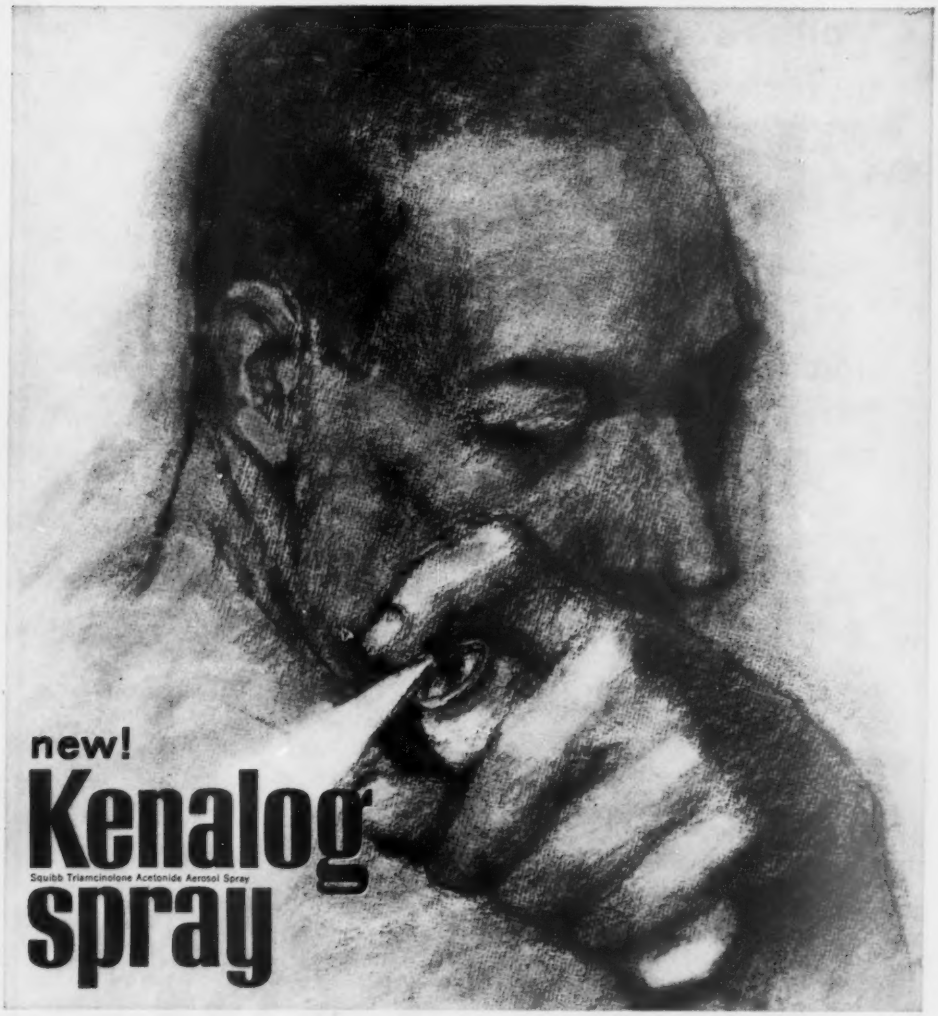
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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:37 (May 2) 1959.

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Indications: Atopic dermatitis, contact dermatitis, eczematous dermatitis, neurodermatitis, seborrheic dermatitis, insect bites, pruritus ani and vulvae, lichen simplex chronicus, exfoliative dermatitis, stasis dermatitis, nummular eczema, sunburn.

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References: 1. Reports to the Squibb Institute for Medical Research. 2. Howell, C. M.: Squibb Clin. Res. Notes *1*:5 (Oct.) 1958. 3. Goodman, J. J.: Squibb Clin. Res. Notes *1*:1 (Oct.) 1958. 4. Smith, J. G., Jr.; Zawisza, R. J., and Blank, H.: Squibb Clin. Res. Notes *1*:6 (Oct.) 1958. 5. Fitzpatrick, T. B.; Crowe, F. W., and Walker, S. A.: Squibb Clin. Res. Notes *1*:1 (Oct.) 1958. 6. Lerner, A. B.: Squibb Clin. Res. Notes *1*:2 (Oct.) 1958. 7. Robinson, R. C. V.: Bull. School of Med., U. Maryland 43:54 (July) 1958.

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References: **1.** W. Schallek, C. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap., 126*:270, 1959. **2.** W. B. Abrams, I. Roseff, J. Kaufman, L. Goldman and A. Bernstein, to be published. **3.** I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp., 9*:189, 1958. **4.** O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **5.** J. A. Lucinian, *ibid.* **6.** D. W. Molander, *ibid.* **7.** B. I. Shnider, *ibid.* **8.** W. S. Derrick, *ibid.* **9.** B. Wolfson and F. F. Foldes, *ibid.* **10.** L. McLaughlin, *ibid.* **11.** Reports on file, Roche Laboratories. **12.** Personal communications. **13.** W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **14.** H. E. Davis, *ibid.*

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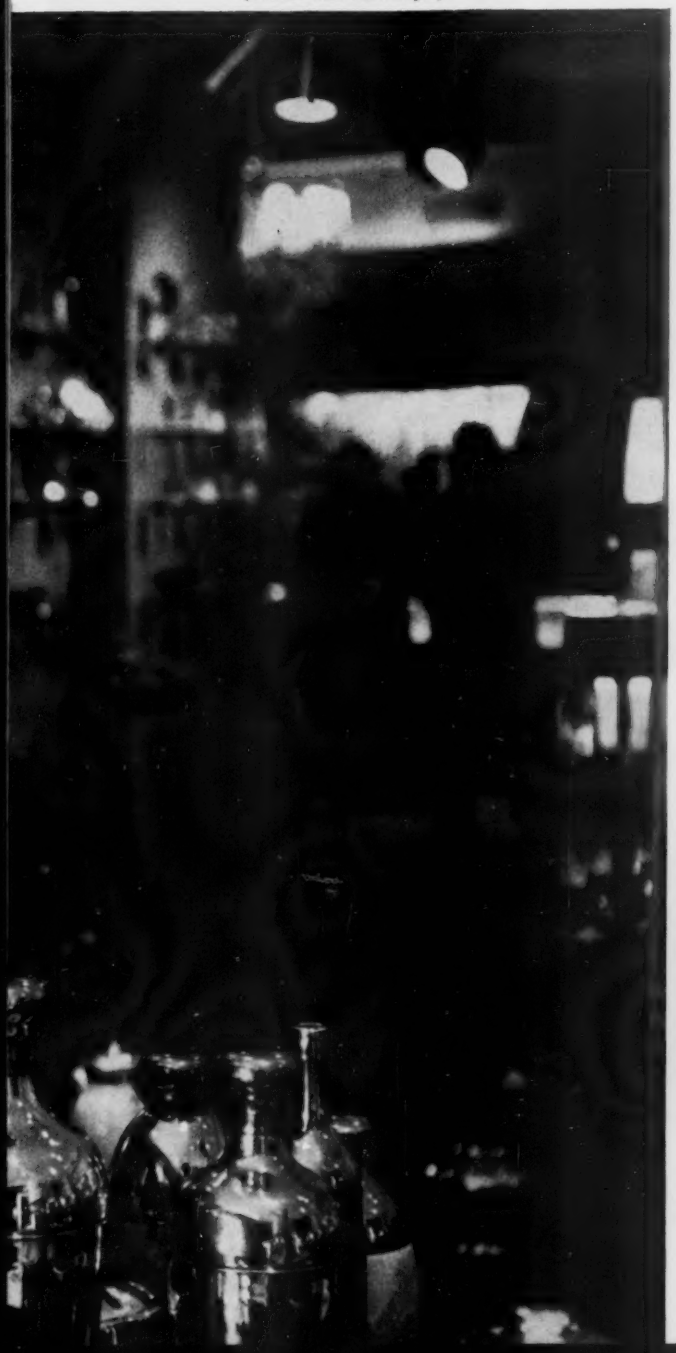
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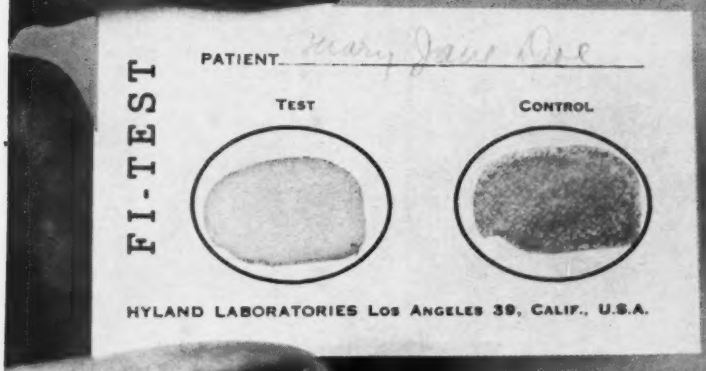
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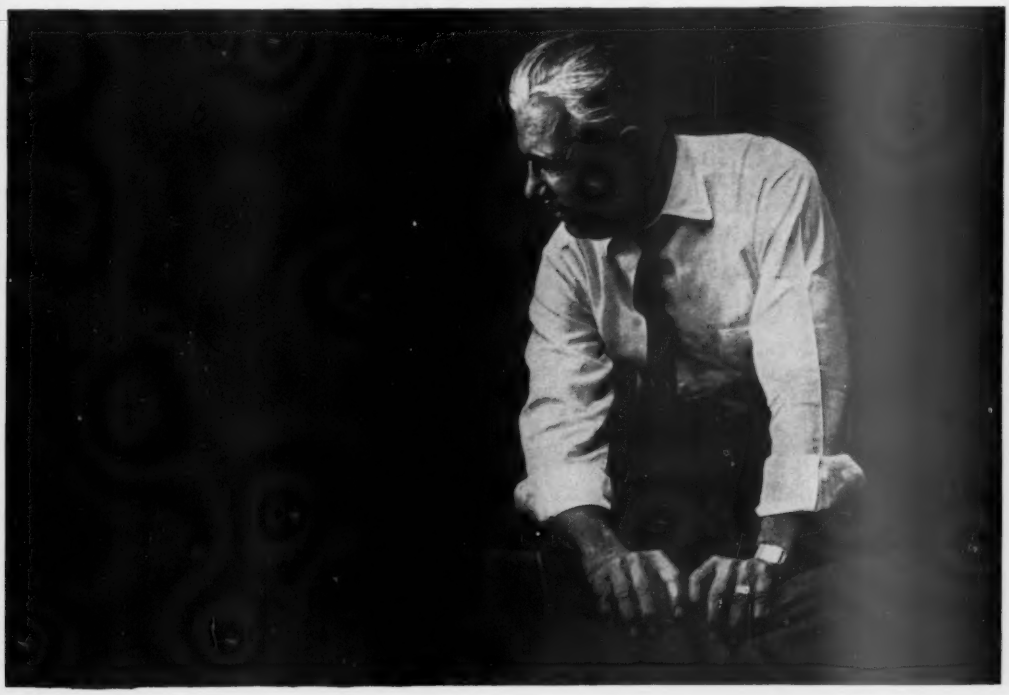
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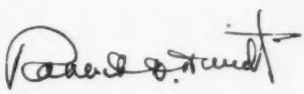
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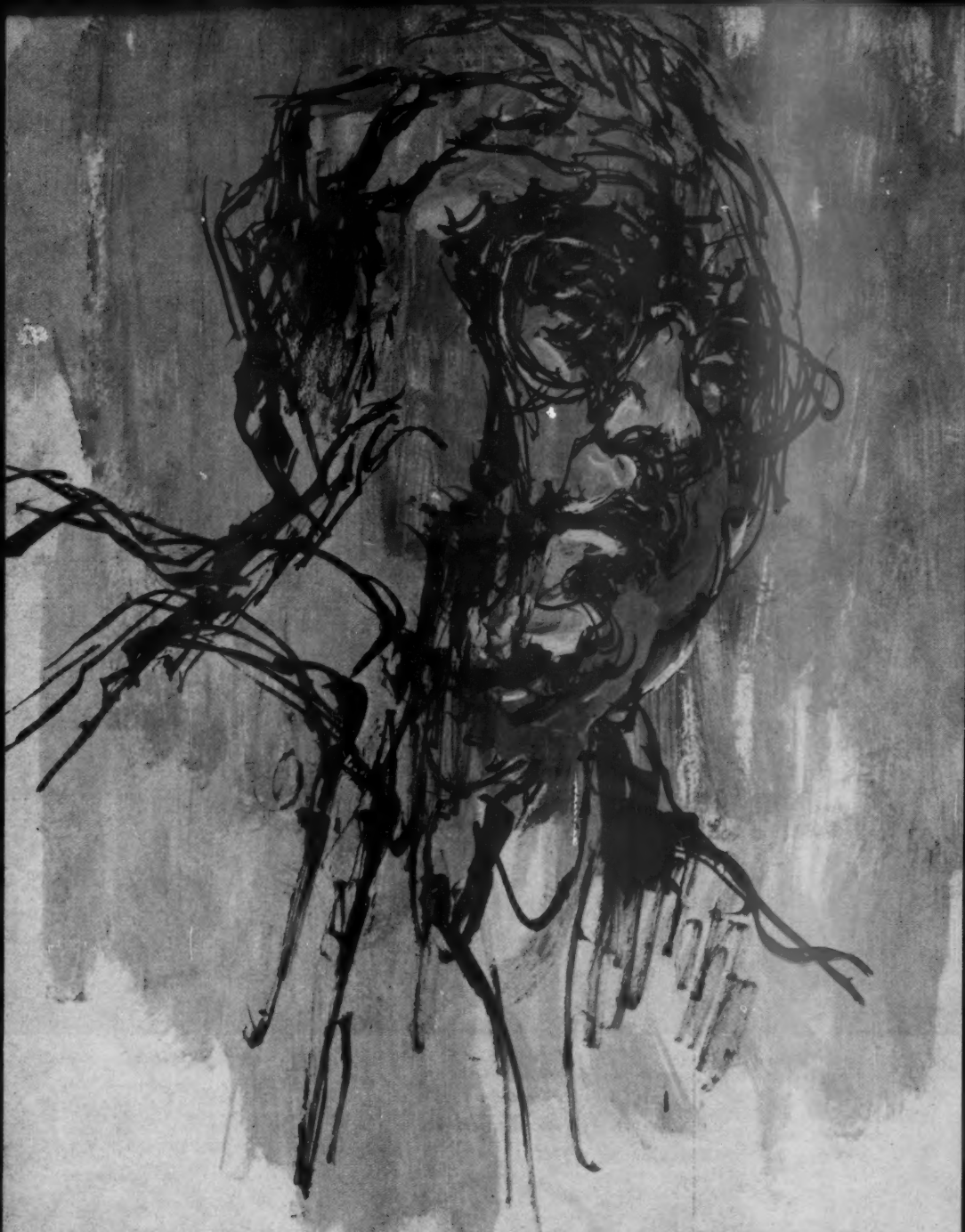
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When you see symptoms of hypertension such as dizziness, headache, and fainting your patient is a candidate for Serpasil-Apresoline. Even when single-drug therapy fails, Serpasil-Apresoline frequently can bring blood pressure down to near-normal levels, reduce rapid heart rate, allay anxiety.

SUPPLIED: Tablets #2 (standard-strength, scored), each containing 0.2 mg. Serpasil and 50 mg. Apresoline hydrochloride; Tablets #1 (half-strength, scored), each containing 0.1 mg. Serpasil and 25 mg. Apresoline hydrochloride.

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hydrochloride (reserpine and hydralazine hydrochloride CIBA)

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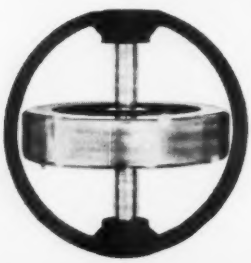
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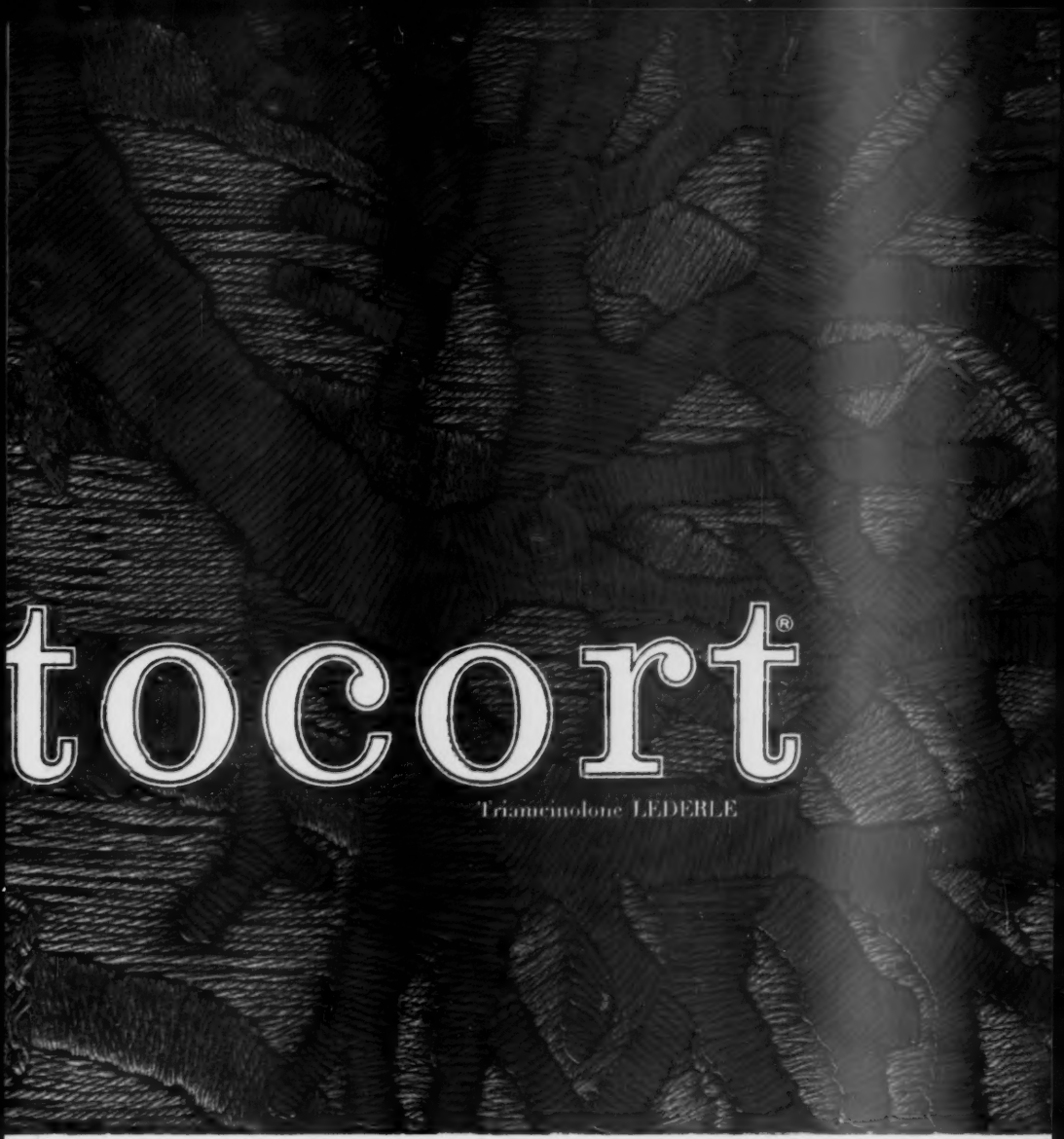
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Substantiated by published reports of leading clinicians

- **effective control** of allergic and inflammatory symptoms[1-8]



- **minimal disturbance** of the patient's chemical and psychic balance[1, 4, 5, 8-18]



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Diacetate Parenteral (for intra-articular and intrasynovial injection). Vials of 5 cc. (25 mg./cc.).

List of References 1-18 supplied on request.

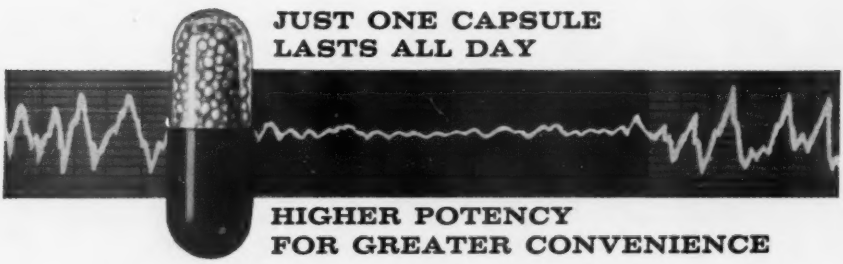
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*Archambault, R.: Canad. M. A. J. *81*:28, 1959.

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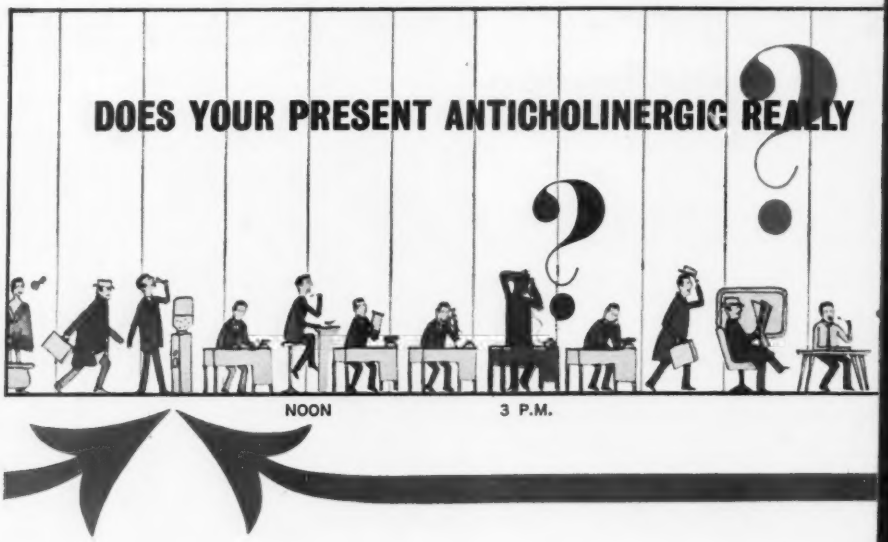
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McHardy: "[Oxyphencyclimine] has proved to be an excellent sustained-action anticholinergic in our study of this agent over a period of eighteen months."[1]

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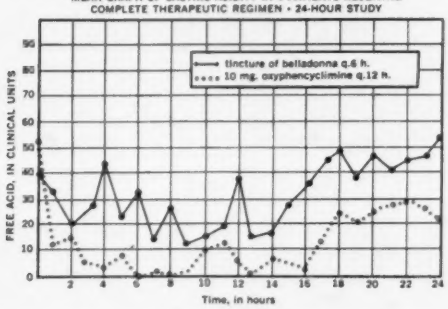
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Clinical Results: Effective in over 92% of cases.

As for Safety: "Side reactions were uncommon, usually no more than dryness of the mouth. . . ."[4]

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Oxyphencyclimine HCl ..... 10 mg.
Hydroxyzine (ATARAX®) ..... 25 mg.

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Supplied: In bottles of 60 black-and-white scored tablets.

References: 1. McHardy, G., et al.: J. Louisiana M. Soc. 111:290 (Aug.) 1959. 2. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois, in press. 3. Kemp, J. A.: Antibiotic Med. & Clin. Therapy 6:534 (Sept.) 1959. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 5. Data in Roerig Medical Department files.

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*Diseases of the Colon & Rectum, Vol. 1, No. 5, Sept.-Oct. 1958.

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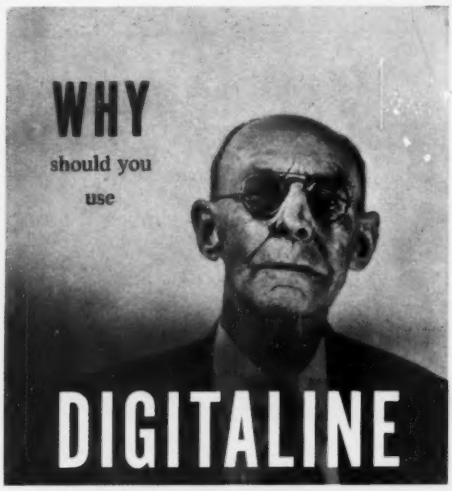
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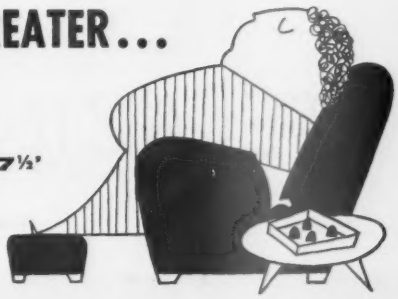
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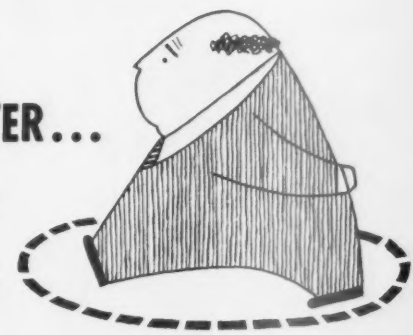
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1. Goddard, E.S.: in *Trifluoperazine, Further Clinical and Laboratory Studies*, Philadelphia, Lea & Febiger, 1959.

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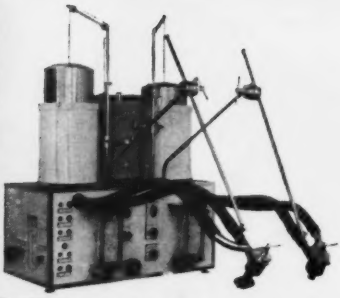
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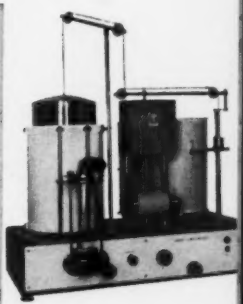
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***Schneider, H.C.: In Press, J. Intern. Coll. Surgeons*

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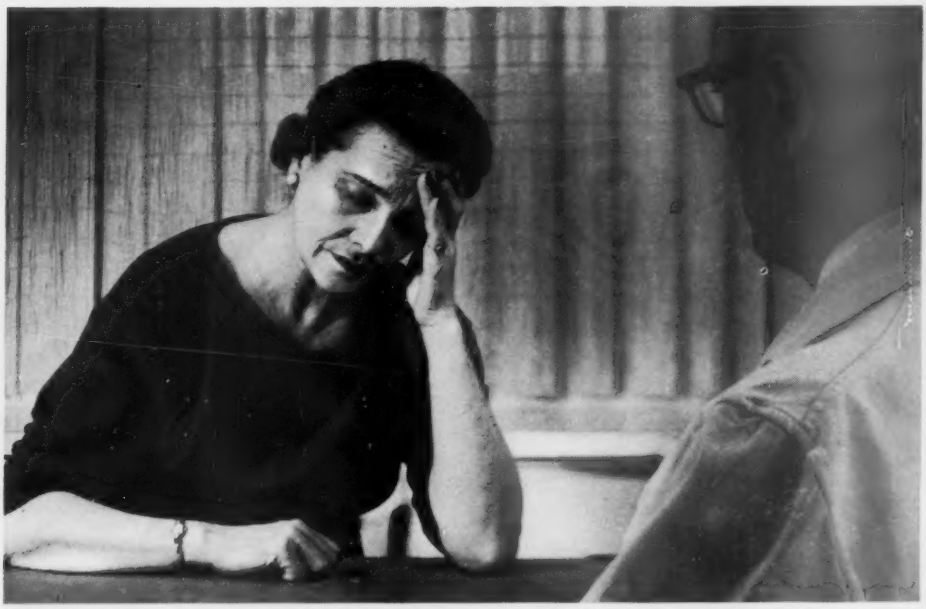
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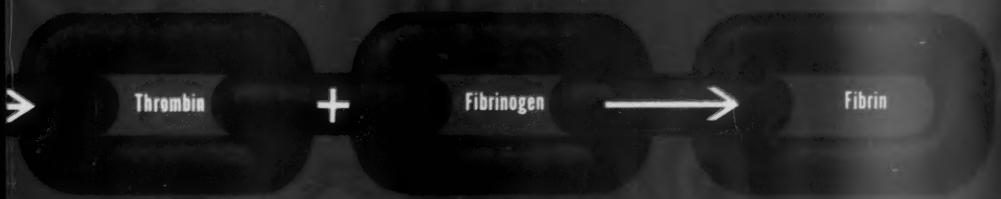
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Council on Drugs, A.M.A. Committee on Therapeutics and Pharmacy, Philadelphia, J. B. Lippincott Co., 1949, p. 318



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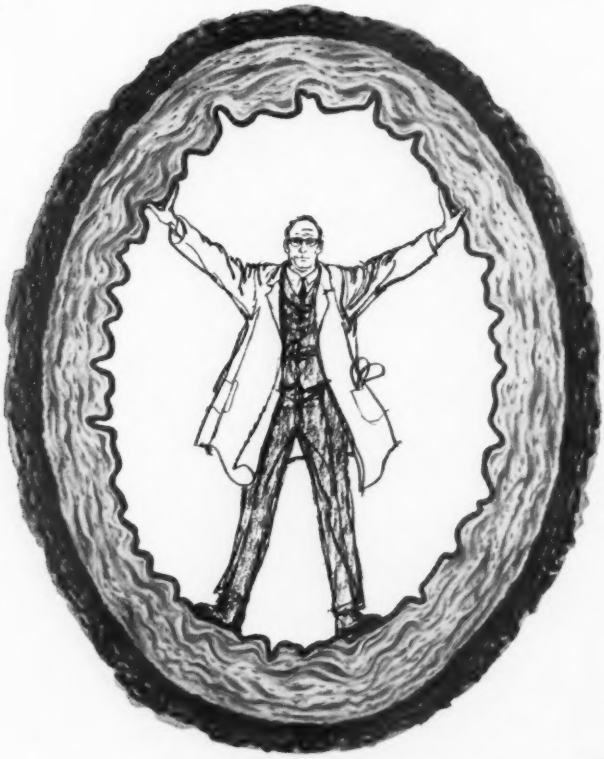
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1. Melville, K. I., and Lu, F.C.: Canadian M.A.J., *65*:11, 1951. 2. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap., *83*:367, 1946. 3. Fuller, H. L., and Kassel, L.E.: Antibiotic Med. & Clin. Therapy, *3*:322, 1956.

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Analexin (phenyramidol HCl) is a new class of drug . . . the first analgomylaxant . . . a single chemical that inherently possesses two different pharmacologic actions within one molecular structure: i.e. (1) *general analgesia*, by raising the pain threshold and thus decreasing perception of pain, and (2) *muscle relaxation*, by selectively depressing subcortical and spinal polysynaptic transmission (interneuronal blockade), abolishing abnormal muscle tone without impairing neuromuscular function.[1-4] Thus, in painful states Analexin abolishes the pain and the muscle tensions which often augment it and manages the total pain experience more effectively.

with remarkably few side effects

Analexin is not related to any currently available analgesic or muscle relaxant drug. The analgesic potency of one tablet is clinically equivalent to 1 grain of codeine, yet Analexin is neither narcotic nor is it narcotic-related. It is not habituating. There is no evidence suggestive of tolerance or cumulative effects. Muscle relaxant action is comparable to the most potent oral muscle relaxants available.[3,4] The incidence of side effects is low and those reactions that have been reported (gastrointestinal irritation, pruritus) are of a mild and transient nature and do not limit therapy.[5]

Analexin . . . *for relief of pain and muscle tension.* Each tablet contains 200 mg. of phenyramidol HCl. Dosage—1 or 2 tablets every 4 hours.

Analexin-AF . . . *for relief of pain and muscle tension complicated by fever and/or inflammation.* Each tablet contains 100 mg. of phenyramidol HCl and 300 mg. of aluminum aspirin. Dosage—2 tablets every 4 hours or as required.



typical results with Analexin* and Analexin-AF in abdominal and pelvic pain[5-8]

Condition	No. Patients	Relief	Slight or no relief
pain associated with:			
duodenal ulcer	10	9	1
hiatus hernia	1	1	
gallbladder colic	5	2	3
dysmenorrhea	96	88	8
abdominal distress (flatulence, colic, constipation, etc.)	10	6	4
epigastric distress (pylorospasm, gastritis, etc.)	10	7	3
genitourinary pain	3	3	
pelvic pain (chronic P.I.D., endometriosis, etc.)	12	8	4
postpartum pain	100	100	
Totals	247	224	23

*Generically designated as phenyramidol HCl in clinical trials

typical comments from investigators

"Not only is satisfactory relief of painful states achieved in the majority of patients regardless of etiology and duration of pain, but there is also no evidence suggestive of cumulative toxicity. Furthermore, in contrast to codeine and meperidine, the likelihood of untoward reactions occurring in ambulant patients is not high."[5]

When phenyramidol with aspirin was used to replace aspirin and codeine, ". . . Codeine grains ½ with aspirin grains 10. Its clinical effectiveness was exactly the same as the former two agents combined."[6]

The patients with duodenal ulcer ". . . presented an excellent symptomatic control of their complaints. These patients were previously under treatment with antacids, antispasmodics and sedatives with recurrent pain and unsatisfactory control. Phenyramidol usually administered alone but occasionally with an antacid resulted in control of 9 of the 10 patients."[7]

REFERENCES: 1. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 2. O'Dell, T. B., *et al.*: Fed. Proc. *18*:694, 1959. 3. Gray, A. P., and Heitmeier, D. E.: J. Am. Chem. Soc. *81*:4347, 1959. 4. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4351, 1959. 5. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959. 6. 511:5912, Clinical Data from the files of the Medical Department, Irwin, Neisler & Co., 1959. 7. Batterman, R. C.: Paper presented at the New York Academy of Sciences Symposium on "Non-narcotic Drugs for the Relief of Pain," Dec. 4, 1959. 8. Wainer, A. S.: Paper presented at the New York Academy of Sciences Symposium, Dec. 5, 1959.

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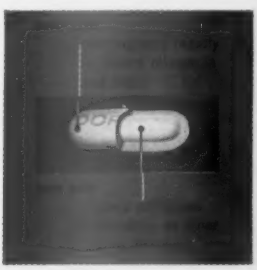
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FOR A FULL NIGHT'S SLEEP

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Might as well try to put a tiger to bed (and keep him there) as to get most patients to sleep naturally all night. For disturbed, interrupted sleep is the most common sleep problem in routine practice. NEBRALIN — a timed-release tablet — encourages muscular relaxation and sustained, relaxed sleep. The combination of mephenesin and Dorsital* in NEBRALIN not only relaxes skeletal muscles, overcomes "fatigue-tension" and conditions the body for sleep, but also induces sound, relaxed sleep by gentle CNS sedation. Mephenesin is capable of producing sleep,[1] and when combined with a barbiturate enhances barbiturate action.[2,3] Moreover, the integrated action of the two components permits smaller dosage of each.[4] Thus, NEBRALIN—a gentle relaxant-sedative—avoids morning hangover, ***and carries your patients through the middle of the night, especially those patients who complain about waking up at 2 A.M.***

1. Schlesinger, E. B.: Tr. New York Acad. Sc. 2:6 (Nov.) 1948. **2.** Richards, R. K., and Taylor, J. D.: Anesthesiology 17:414, 1956. **3.** Shideman, F. E.: Postgrad. Med. 24:207, 1958. **4.** Berger, F.: Pharmacol. Rev. 1:243, 1949.



Each Nebralin timed-release tablet contains: Dorsital*, 90 mg.; Mephenesin, 425 mg. **Dosage:** One or two tablets ½ hour before retiring. **Supplied:** Bottles of 50 Nebralin timed-release Tablets.

*Dorsey brand of pentobarbital.

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PET *Instant* instead of whole milk for drinking cuts calories in half. Yet it supplies all the essential milk nourishment, except the fat. Used in cooking, it allows the diet to include many foods not permissible when made with whole milk or cream.

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PET *Instant* is a delicious, fresh-tasting beverage—one your patients will enjoy using. It mixes instantly . . . costs only about 8¢ a quart.



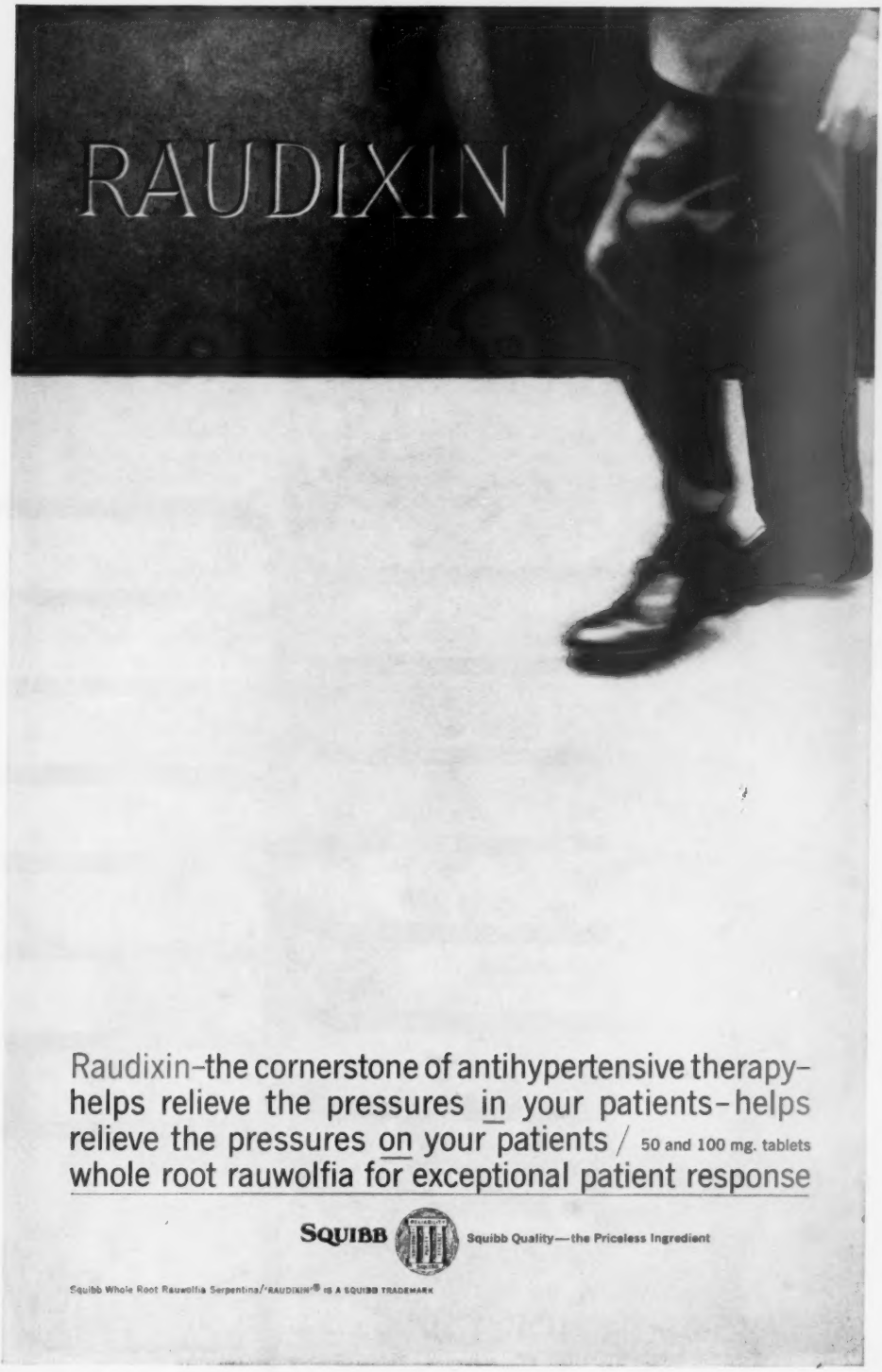
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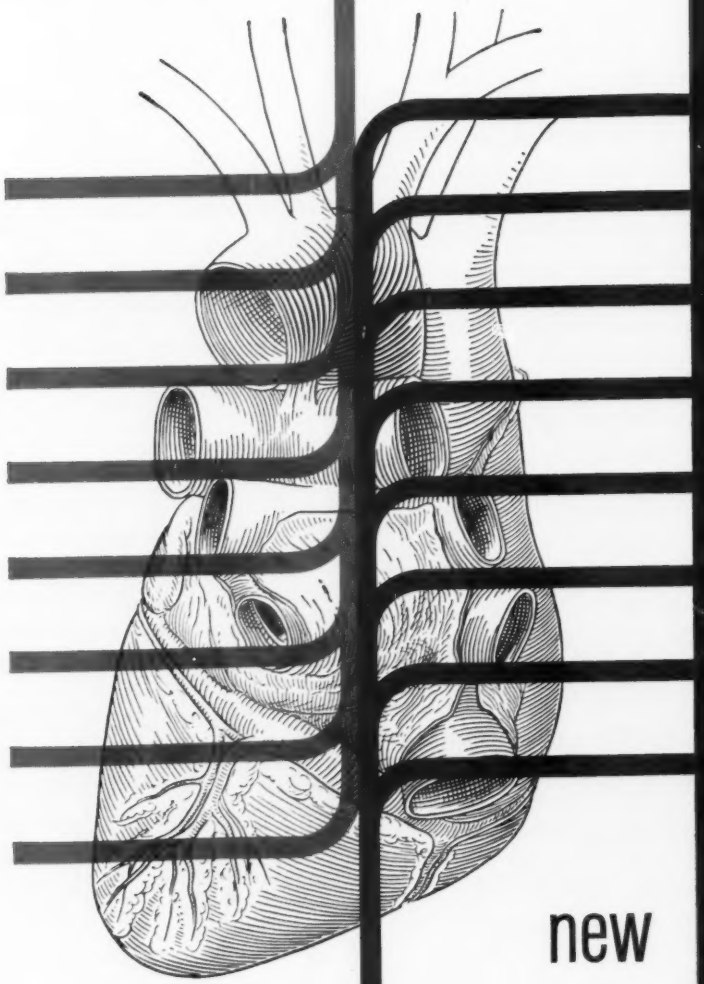
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A recent Marplan report from the literature[2]

Patients	*Age*	*Diagnosis*	*Usual Dose*	*Duration of Treatment*
31	40's-70's	Angina pectoris. "About one-half were severely ill."	15-30 mg/day	1-9 mos.

Results: "Over 70 per cent of the patients reported notable benefits. . . ."

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Supplied: 10-mg tablets in bottles of 100 and 1000.

References: 1. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 2. G. C. Griffith, *Clin. Med.*, 6:1555, 1959.

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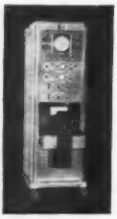
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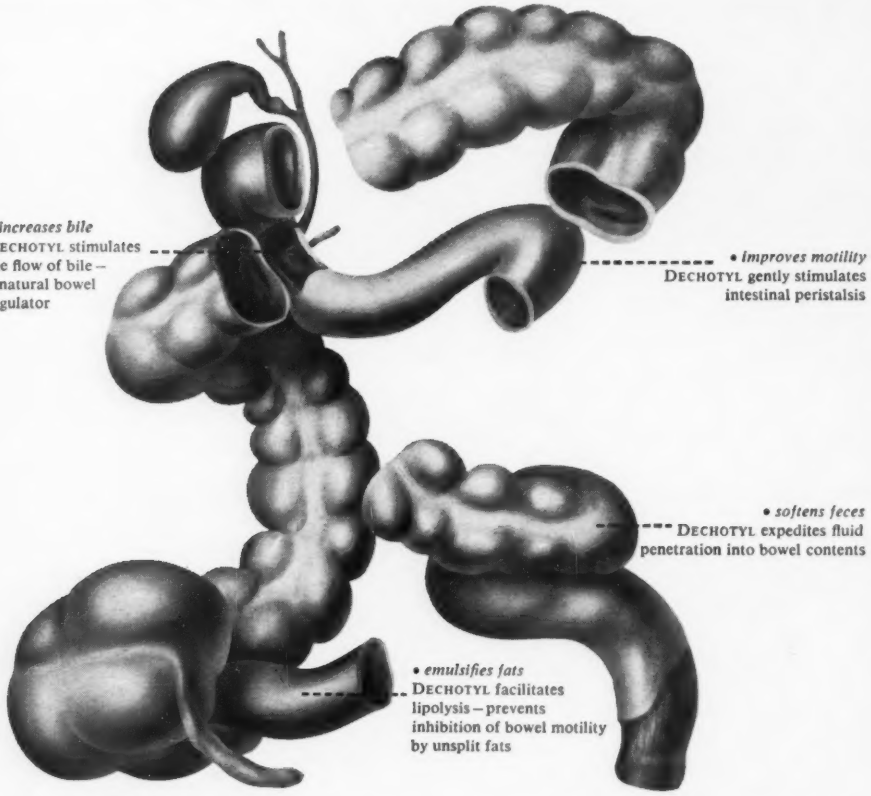
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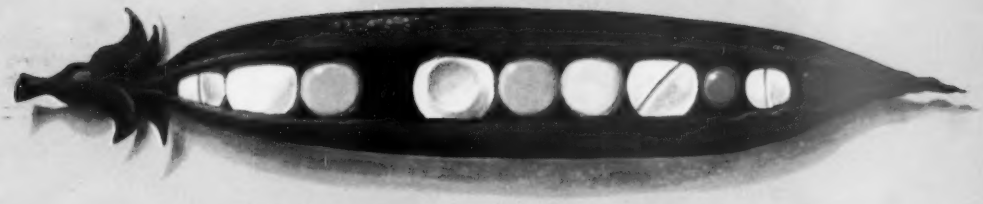
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*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.



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1. Cohen, R. V., Lambert, R. L., and Molthan, L.: The Use of POTABA in Sarcoidosis; Annual Meeting American Trudeau Society, Eastern Section, Boston, Mass. (1958).

2. Zarafonetis, C. J. D., and Horrax, T. M.: Treatment of Peyronie's Disease with POTABA, Journal of Urology, 81: 770-772 (June 1959).

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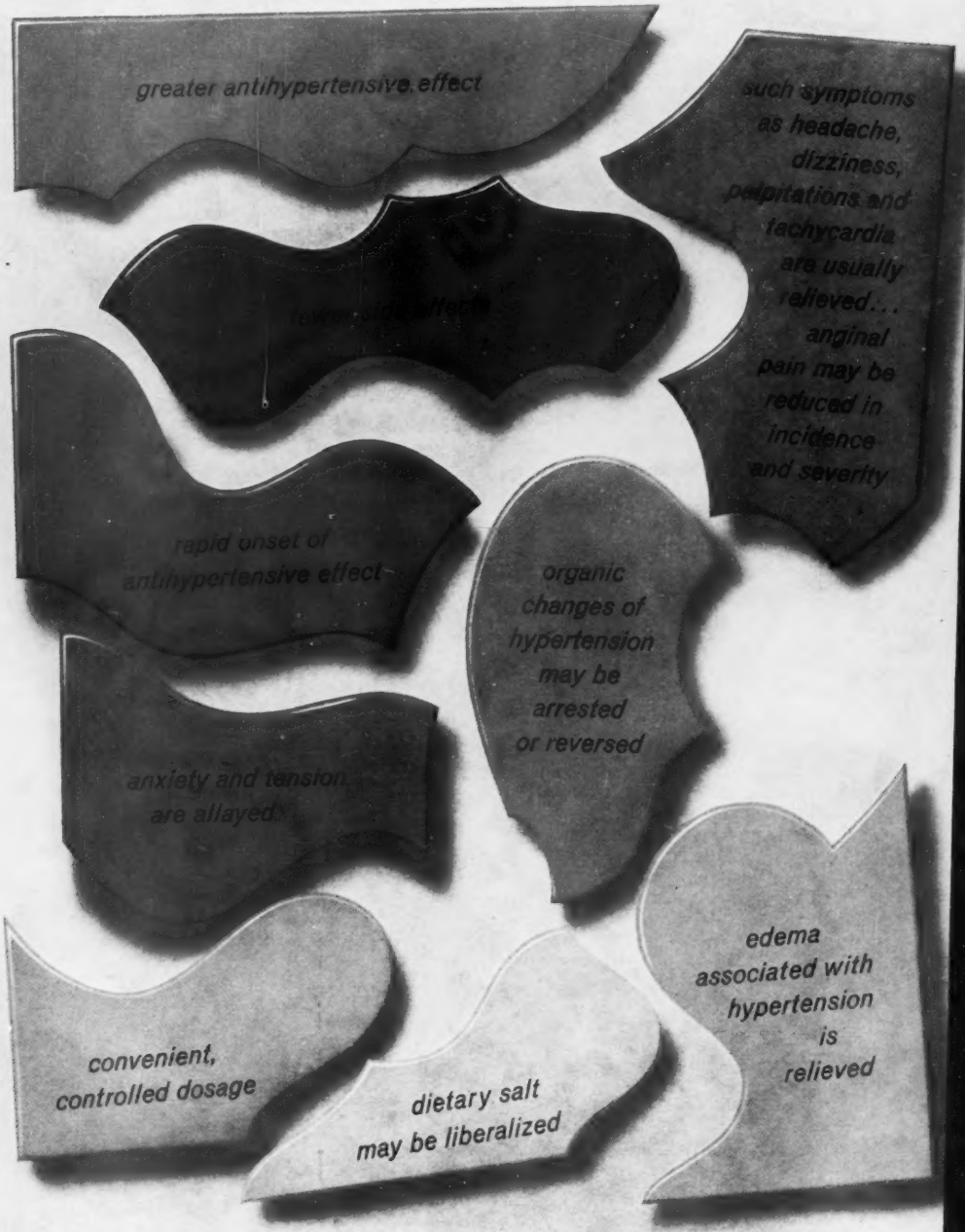
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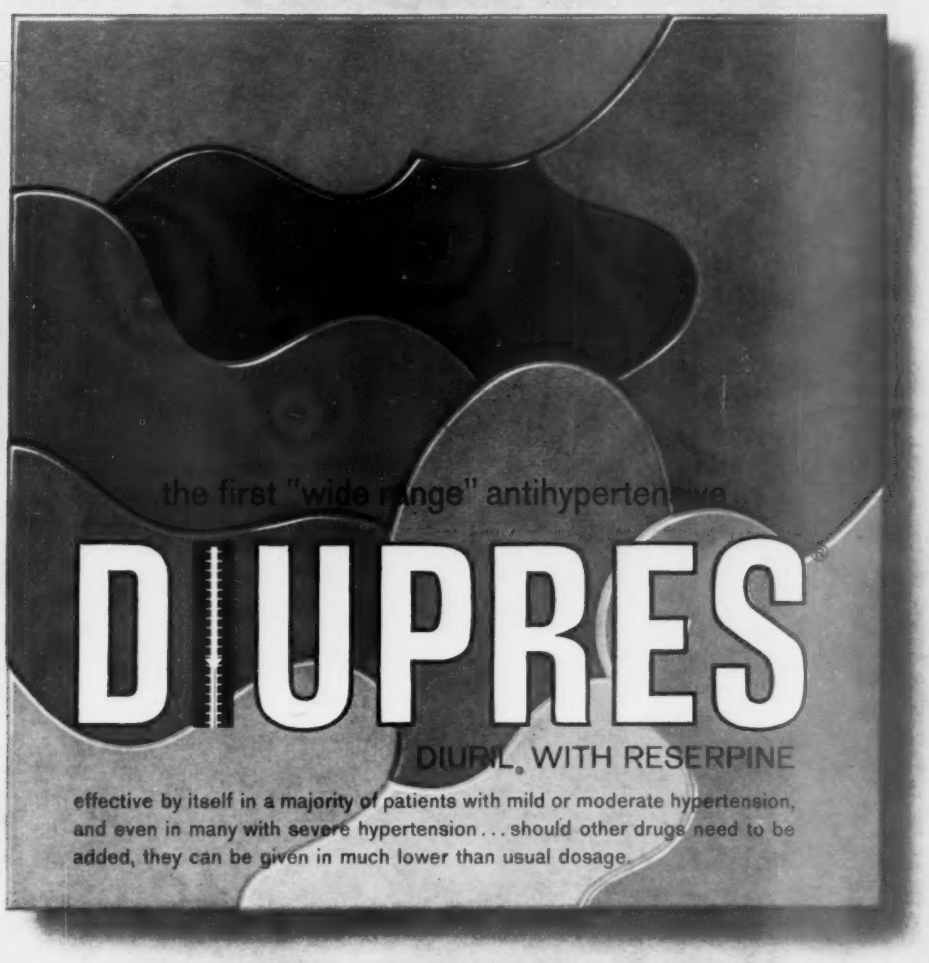
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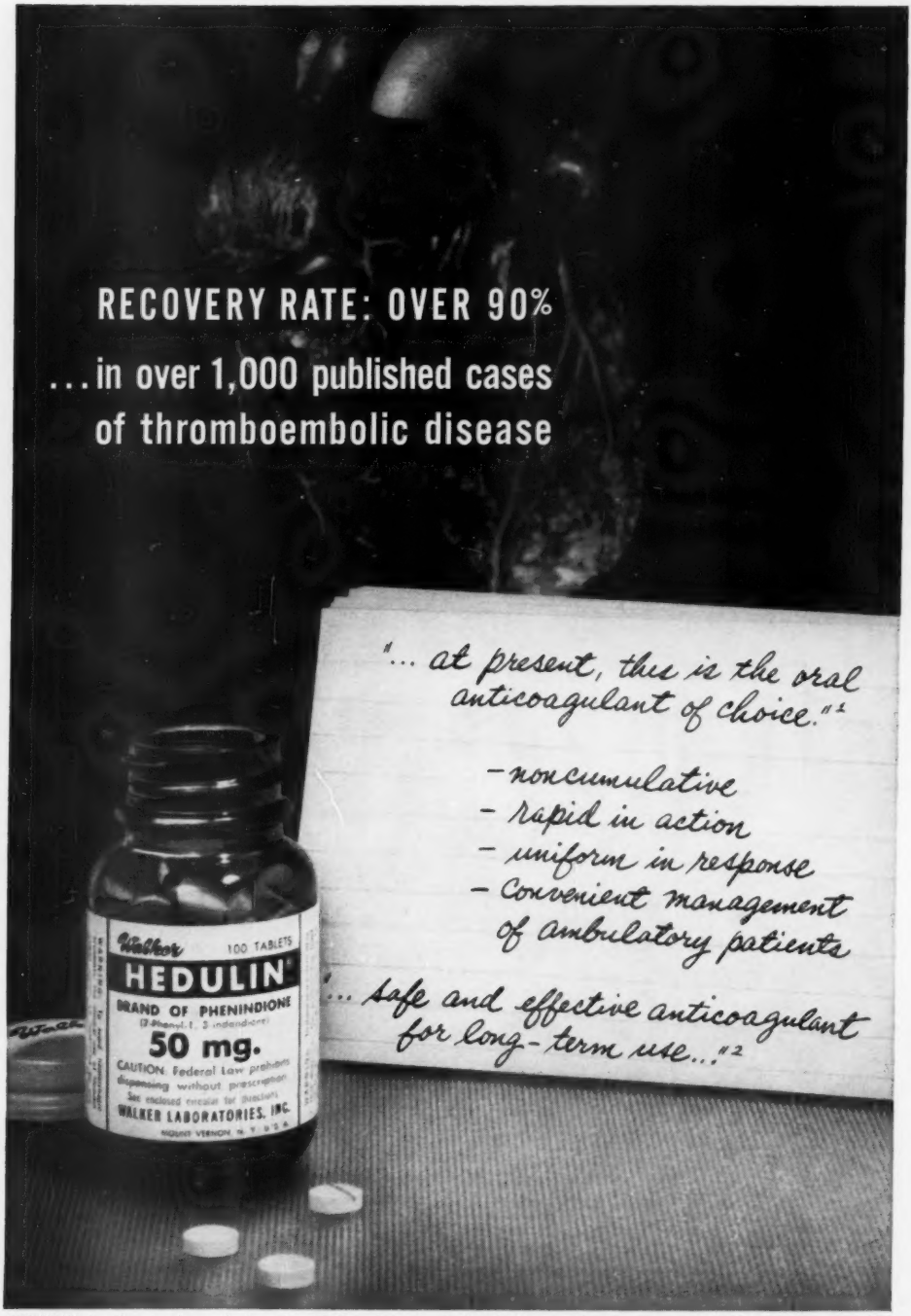
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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Schedule of Postgraduate Courses, Spring, 1960

The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Customary tuition fees will be: members, $60.00; nonmembers, $80.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine St., Philadelphia 4, Pa.

	March		April				May				June			
	21–25	28–April 1	4–8	11–15	18–22	25–29	2–6	9–13	16–20	23–27	May 30–June 3	6–10	13–17	20–24
Course No. 1, RECENT ADVANCES IN PHARMACOTHERAPY: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director.	X		A.C.P. Annual Session, San Francisco, Calif.										A.M.A. Meeting, Miami, Fla.	
Course No. 2, CURRENT CONCEPTS IN GASTROENTEROLOGY: Tulane and Louisiana State Universities Schools of Medicine, New Orleans, La.; G. Gordon McHardy, M.D., F.A.C.P., Director; Robert L. Simmons, M.D., and Helen Von Fossen, M.D., Associate Directors.		28–31												
Course No. 3, DERMATOLOGY FOR THE INTERNIST: University of Michigan Medical School, Ann Arbor, Mich.; Arthur C. Curtis, M.D., F.A.C.P., Director; E. Richard Harrell, M.D., Co-director.						X								
Course No. 4, THE EARLY DETECTION AND PREVENTION OF DISEASES: University of Pennsylvania School of Medicine, Department of Public Health and Preventive Medicine, Philadelphia, Pa.; John P. Hubbard, M.D., F.A.C.P., and Norbert J. Roberts, M.D., F.A.C.P., Co-directors.								X						
Course No. 5, CURRENT RESEARCH IN CARDIOVASCULAR DISEASES: National Heart Institute, Bethesda, Md.; Luther L. Terry, M.D., F.A.C.P., Director.									X					
Course No. 6, THE HYPERTENSIVE DISEASES: DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN ESSENTIAL, ADRENAL AND RENAL HYPERTENSION: Boston University School of Medicine, Massachusetts Memorial Hospitals, Boston, Mass.; Robert W. Wilkins, M.D., F.A.C.P., Director.										23–26				
Course No. 7, INTERNAL MEDICINE: Indiana University School of Medicine, Indianapolis, Ind.; John B. Hickam, M.D., F.A.C.P., Director.														X

The following courses are scheduled for FALL–WINTER, 1960: **HEMATOLOGY and RADIOISOTOPES,** Ohio State Univ. College of Med., Sept. 19–23; **CANCER AND THE INTERNIST,** Memorial Sloan-Kettering Cancer Center, New York, Oct. 10–14; **ELECTROCARDIOGRAPHY,** Univ. of Utah, Nov. 14–19; **INTERNAL MEDICINE,** Univ. of Oklahoma Medical Center, Oklahoma City, Feb. 20–24, 1961.

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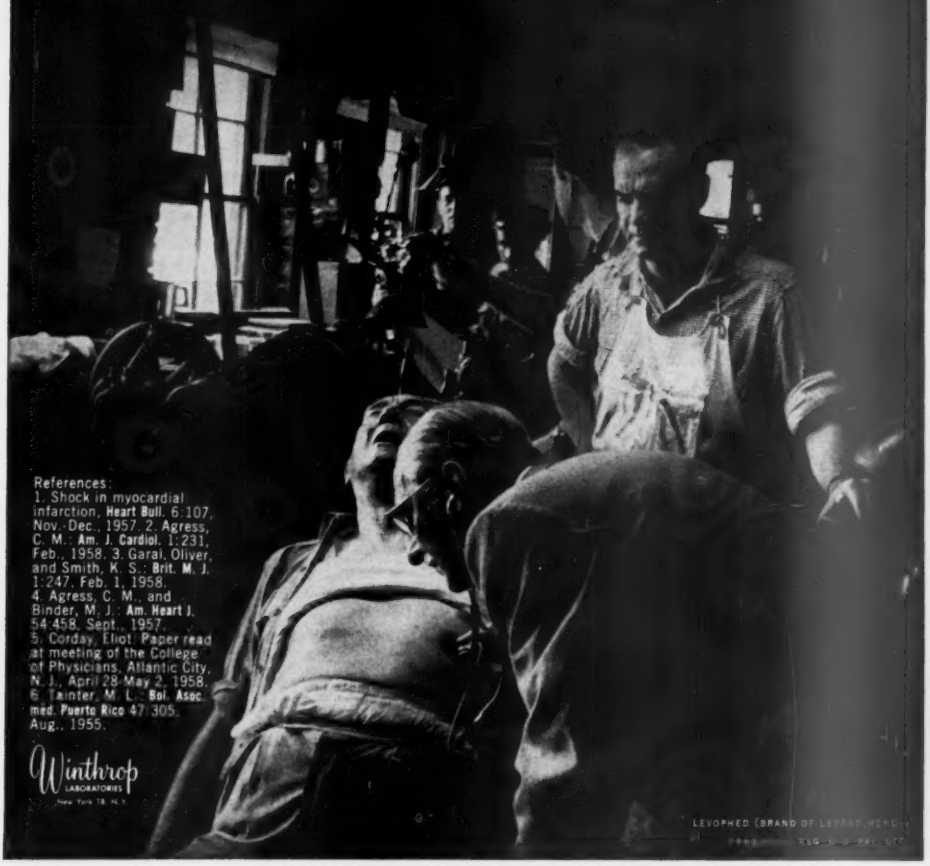
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With the prompt use of Levophed, 28 per cent of patients who would have died of severe coronary shock now live.[6]



References:
1. Shock in myocardial infarction, **Heart Bull.** 6:107, Nov.-Dec., 1957. 2. Agress, C. M.: **Am. J. Cardiol.** 1:231, Feb., 1958. 3. Garai, Oliver, and Smith, K. S.: **Brit. M. J.** 1:247, Feb. 1, 1958. 4. Agress, C. M., and Binder, M. J.: **Am. Heart J.** 54:458, Sept., 1957. 5. Corday, Eliot: Paper read at meeting of the College of Physicians, Atlantic City, N. J., April 28-May 2, 1958. 6. Tainter, M. L.: **Bol. Asoc. med. Puerto Rico** 47:305, Aug., 1955.

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—Sherber[6]

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4 unusual safety The only side effect reported has been transitory, easily controlled headache, normally considered an expression of effective pharmacodynamic activity.[2]

References:
1. Summary of Case Reports on File, Ives-Cameron Company (1958-1959). 2. Riseman, J.E.F., et al.: Circulation *17*:22 (Jan.) 1958. 3. Russek, H.I.: Personal Communication (Oct., 1959). 4. Case Reports on File, Ives-Cameron Company (1958-1959). 5. Albert, A.: Personal Communication (Oct., 1959). 6. Sherber, D.A.: Persona Communication (Oct., 1959).

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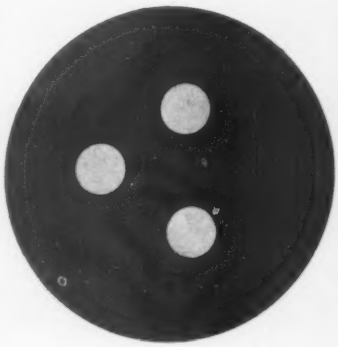
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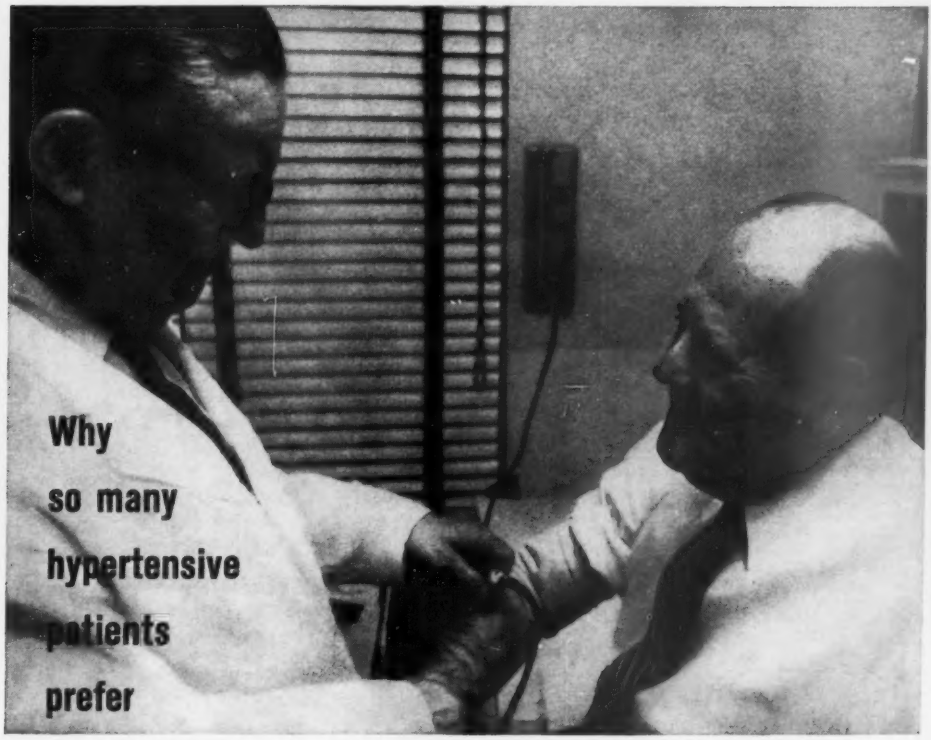
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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

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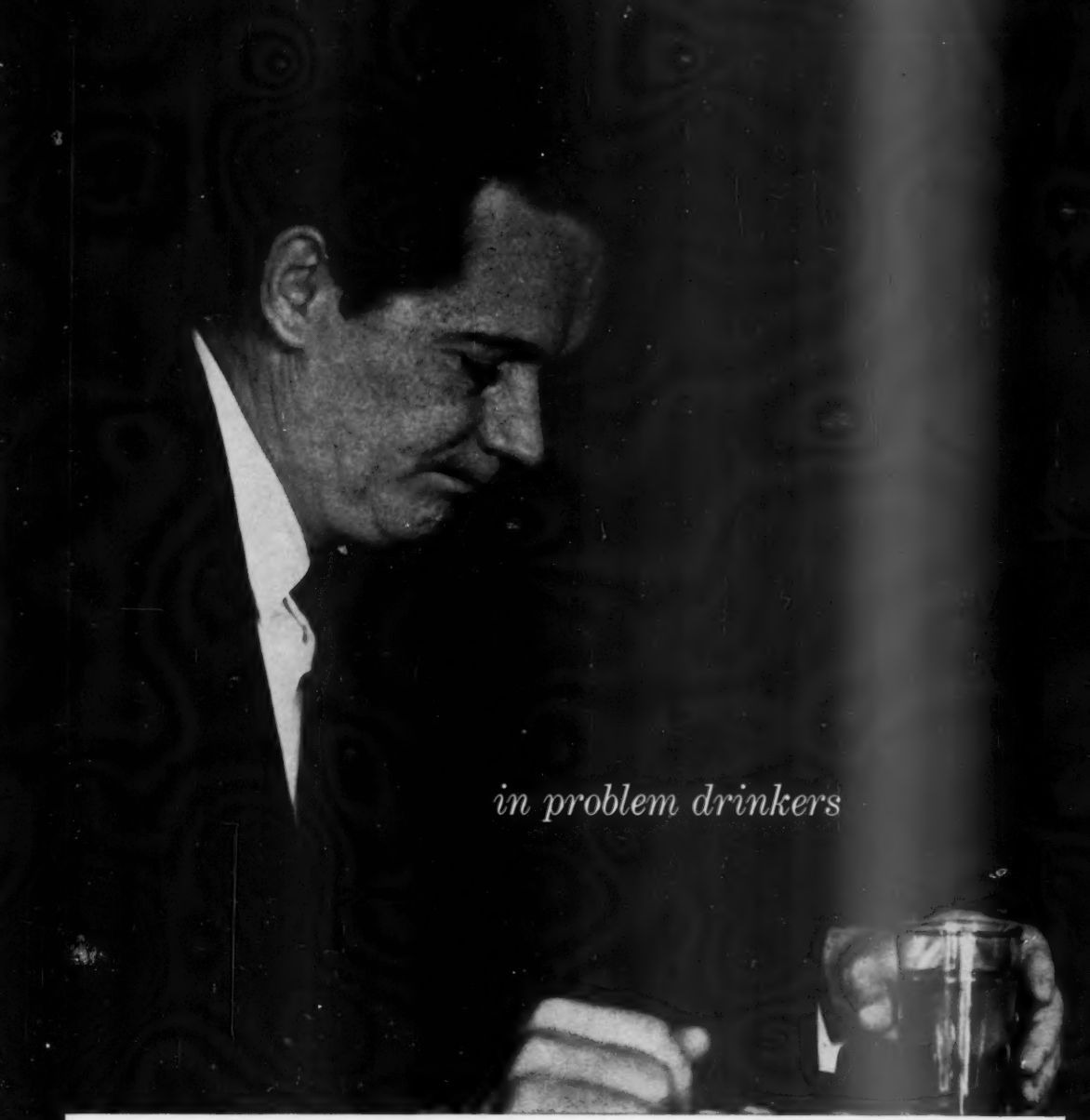
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INDEX TO ADVERTISERS

APRIL, 1960

Abbott Laboratories 20–21, 52–53, 72–73, 112–113
Adolph's Limited 6
A. C. P. Postgraduate Courses 166
Ames Company 32, 158
A. I. M. Jesse Jones Volume File 144
A. I. M. Subscriptions 144
A. I. M. Wanted Back Issues 117, 128
Armour Pharmaceutical Company 27, 54, 121
Astra Pharmaceutical Products, Inc. 103
Ayerst Laboratories 31, 88–89, 116–117, 143
Borcherdt Company 136
Burton, Parsons & Company 78
Cambridge Instrument Company, Inc. 156
Ciba Pharmaceuticals Products, Inc. 12–13, 28–29, 37, 69, 70, 115, 128–129, 171
Crookes-Barnes Laboratories, Inc. 49
Davies Rose & Company, Limited 159
Dietene Company, The 57
Eaton Laboratories 36, 82, 170
Endo Laboratories 22, 100
E. Fougera & Co., Inc. 136
Geigy Chemical Corporation 18, 77, 86, 101, 133
Glenwood Laboratories 160
Grune & Stratton, Inc. 5
Harvard Medical School (Courses for Graduates) 4
Harvard University Press 4
Paul B. Hoeber, Inc. 3
Hyland Laboratories 118
Instrumentation Associates, Inc. 140
Irwin Neisler & Co. ..... Insert facing 148, 149
Ives-Cameron Company 43, 168–169
Knoll Pharmaceutical Company 120
Lakeside Laboratories, Inc. 92–93
LaMotte Chemical Products Company 125
Lederle Laboratories, Div. American Cyanamid Co. 130–131
Thos. Leeming & Company 2, 148
Eli Lilly & Company ..... Third Cover
Macmillan Company, The 1
McNeil Laboratories, Inc. 50, 83
Mead Johnson & Company 110
Medical Protective Company 6
Merck Sharp & Dohme 10, 46–47, 60–61, 95, 122–123, 146–147, 162–163
Wm. S. Merrell Company, The 35
Organon, Inc. 44–45
Parke Davis & Company 102
Pet Milk Company 152
Pfizer Laboratories, Div. Chas. Pfizer Co., Inc. 8, 67, 157, 173
Pharmacia Laboratories, Inc. 31
Pitman-Moore Company 48, 106
Reed & Carnrick 19
Riker Laboratories ..... Second Cover, 59, 174
A. H. Robins Company 15, 63
Roche Laboratories, Div. Hoffmann La Roche, Inc. 80–81, 94, 108–109, 154–155
J. B. Roerig & Company 38, 134–135
Wm. H. Rorer, Inc. 26
Sanborn Company 74
Sandoz Pharmaceuticals ..... Insert facing 164
Schering Corporation 87, 111
Schieffelin & Co. 30
G. D. Searle & Co. 97
Smith-Dorsey Company 75, 150–151
Smith, Kline & French Laboratories 14, 58, 65, 119, 138
E. R. Squibb & Sons, Div. Olin Mathieson Chemical Corp. 33, 42, 49, 55, 90, 107, 114, 125, 153
R. J. Strasenburgh Co. 137, 139
Training School, The 117
Upjohn Company, The 16–17, 62
U. S. Vitamin Corporation 40–41
Walker Laboratories, Inc. 164
Wallace Laboratories 24–25, 51, 76, 91, 95, 104–105, 132, 145, 165
Warner-Chilcott Laboratories 7, 9, 66, 70, 84–85, 142
Warren-Teed Products, Inc. 68
White Laboratories, Inc. 39, 126
Winthrop Laboratories, Inc. 167
Woodward Medical Personnel Bureau 125
Wyeth Laboratories ..... Insert facing 48, 11, 23, 56, 64, 71, 98–99, 127, 141, 161
Wynn Pharmacal Corporation 124



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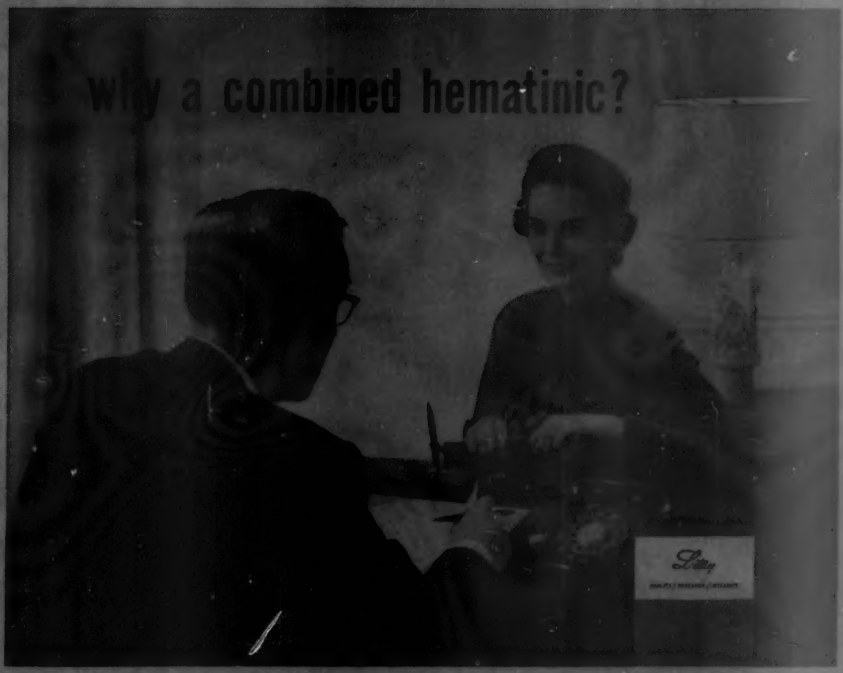
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1. A. M. A. Arch. Int. Med., *99*:346, 1957.
2. Am. J. Obst. & Gynec., *70*:1309, 1955.
3. Lancet, *1*:448, 1957.

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